Kronik Yarada Yardımcı Tedavi Yöntemleri

Büyüme Faktörleri
Negatif Basınçlı Yara Tedavisi

Alper ŞENER

Diyabetik ayak ülseri varlığı 5 yıllık mortaliteyi 2.5 kat arttıyor

Walsh JW, Hoffstad OJ, Sullivan MO, Margolis DJ. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. Diabet Med 2016;33:1493-8.

Diyabetik ayak ülserlerinin >%50 enfekte…

Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54(12): e132-e173. 12.

Orta / Ağır Diyabetik ayak enfeksiyonlarının ortalama %20'si ampütasyon ile sonuçlanıyor…

Ülsere eşlik eden periferik arter hastalığı enfeksiyon ve ampütasyon riskinin arttıran en önemli bağımsız risk faktörü

Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med. 2017 Jun 15;376(24):2367-2375. doi: 10.1056/NEJMra1615439. PMID: 28614678.

Basit ülserlerde 5 yıllık mortalite %30, amputasyon sonrası mortalite %70, renal replasman tedavisi alanlarda 2 yıllık mortalite %74…

Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic Foot Ulcers: A Review. JAMA. 2023 Jul 3;330(1):62-75. doi: 10.1001/jama.2023.10578. PMID: 37395769; PMCID: PMC10723802.

ABD-diyabetik ayak ülserinin yıllık tedavi maliyeti 9-13 milyar dolar

22.3 milyon DM hastası, 245 milyar dolar ilaç-tedavi gideri…176 milyar dolar sağlık, 69 milyar dolar iş gücü kaybı

Tedavi maliyeti diyabetik ayak ülseri

- İlk tanı anında ortalama 4,595 ile 35,000 dolar
- Ülser varlığı göre ortalama yıllık hasta başına 11,710- 16,883 dolar ek maliyet

Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. Diabetes Care. 2014;37(3):651-8. doi: 10.2337/dc13-2176. Epub 2013 Nov 1. Erratum in: Diabetes Care. 2014 Sep;37(9):2660. PMID: 24186882.

YARANIN TAM KAT KAPANMASI

S

SOSYAL FAKTÖRLER

R

REJENERASYON-HÜCRESEL AKTİVİTE

E

EPİTELİZASYONUN UYARILMASI

M

NEM DENGESİNİN SAĞLANMASI

I

ENFEKSİYON -ENFLAMASYONUN KONTROLÜ

T

DOKU YÖNETİMİ-DEBRİDMAN-REVASKÜLERİZASYON

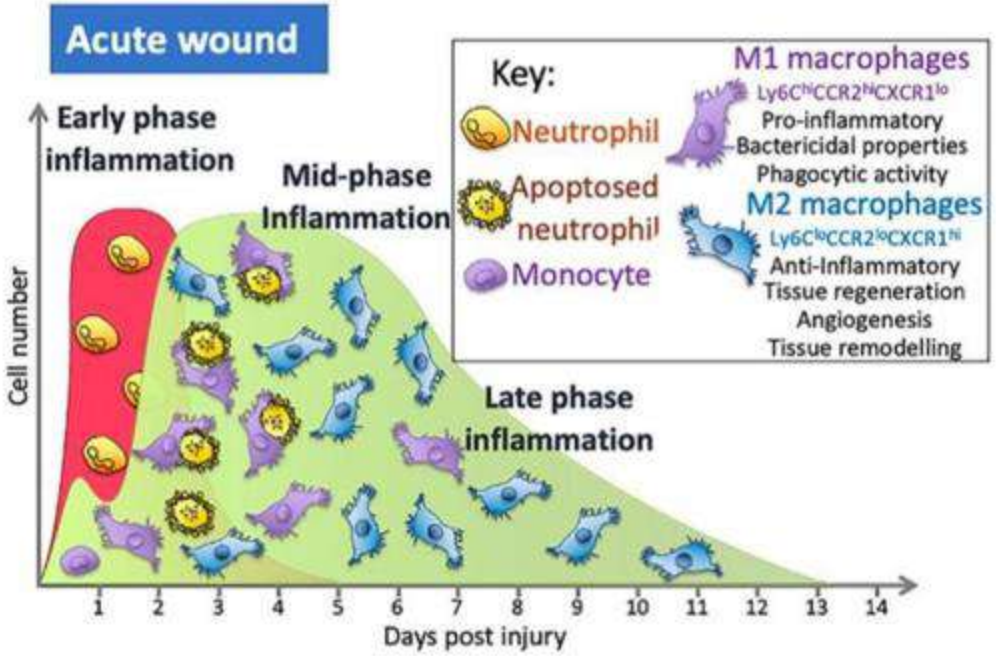
Konvansiyonel ülser tedavisi?

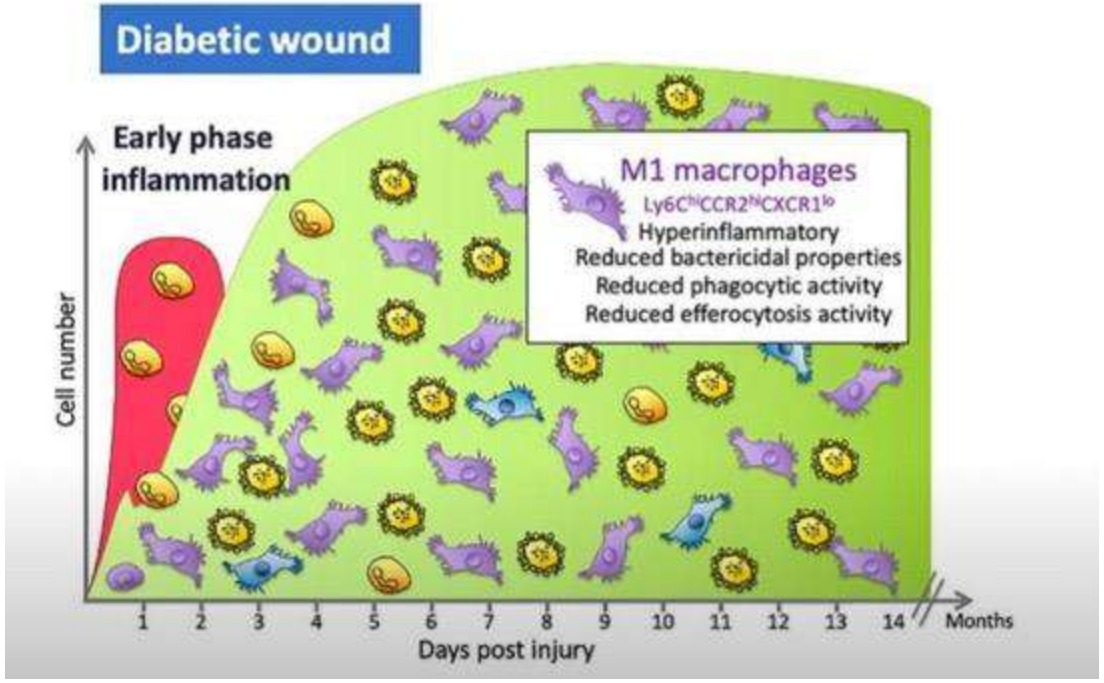
- Medikal…AB, antiagregan, KŞ regülasyonu…
- Cerrahi…debridman, flap, graft…ampütasyon…
- Makrovasküler onarım… girişimsel kapalı, açık cerrahi…
- Mikrovasküler onarım?
- Nöropati…ağrı varsa…medikal, cerrahi
- Nöroprotektif ? Nöropreservatif yöntemler?
- Yükten kurtarma…
- Eğitim…hasta, yakını…
- Pansumanlar ve diğer yöntemler …

İleri düzey yara bakım/tedavisi?

- HBO
- Doku iskeletleri
- Büyüme faktörleri
- TWOT
- Plazma
- Hücresel tedaviler

Bir yara neden iyileşmez?

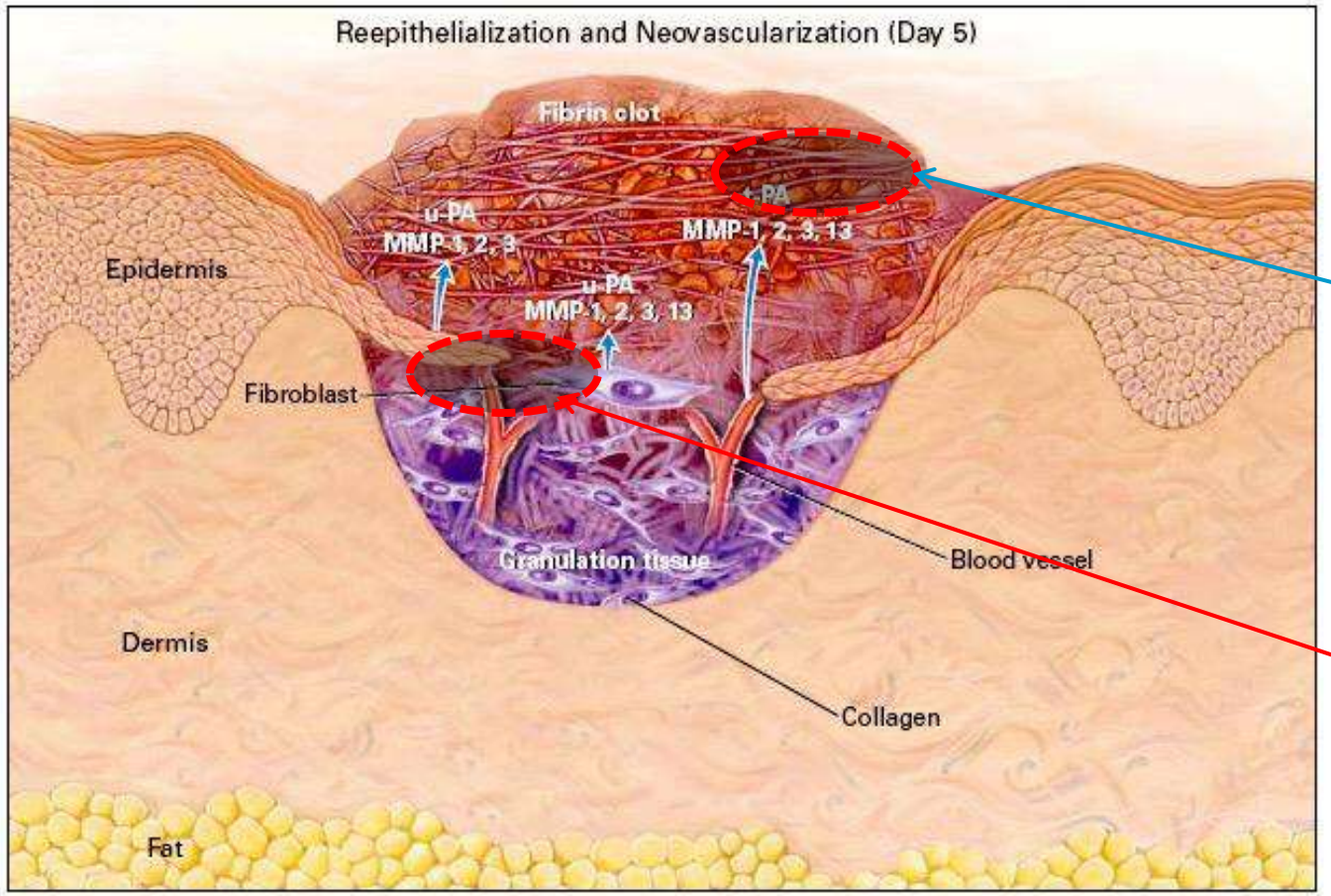




- Nötrofil, mast hücre artışı, inflamatuar yanıt artışı
- Arteriyel okluzyon ve mikrosirkulasyon yetmezliği
- Mikrosirkülasyonda kaçaklar
- Angiogenez bozulması…
- Fibroblast aktivitesi bozulması…
- Hipoksik doku hasarı… oksidatif stress
- ECM organizasyonu kötü, persistan inflamasyon
- M2 ye dönüş azalması…bozulmuş fibroblast aktivitesi

Kronik Yarada Oksijen Seviyesi Düşüktür

- Hipoksik ortam
- Biyofilm
- Fibrinöz eksüda
- Bozulmuş granülasyon
- Doku yıkım enzimleri (sitokromoksidaz, matriks metalloproteinaz, kollajenaz, hyalülonidaz)
- Yarım-yamalak oluşan kollajen lerin yıkımı…



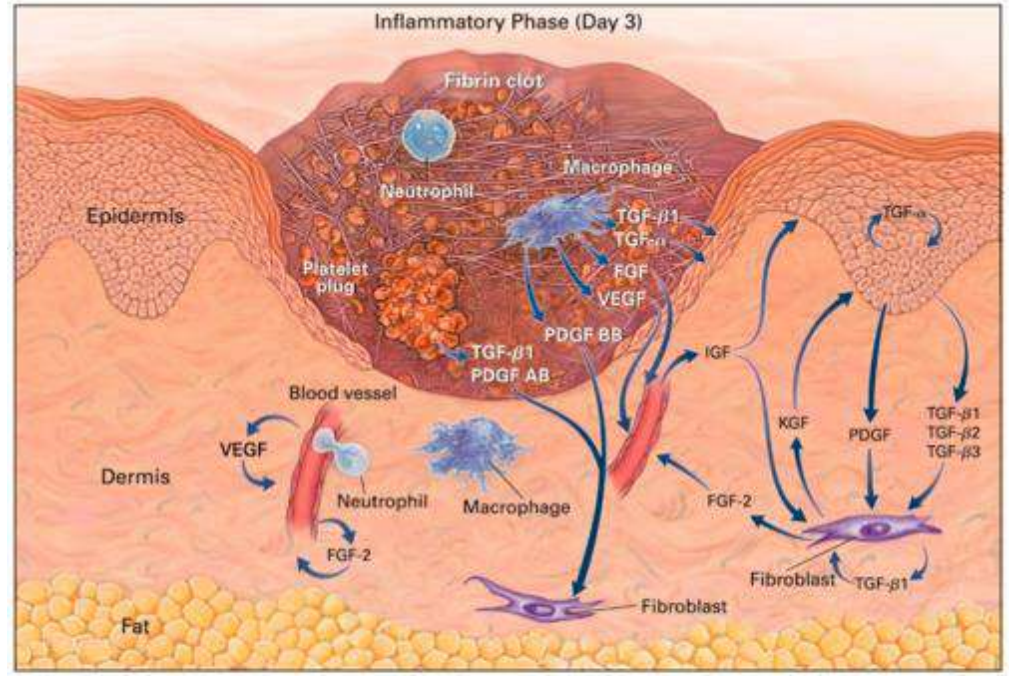
Yara yüzeyindeki pO_2 60 mmHg

Yara merkezindeki pO_2 <10 mmHg

Source: Singer & Clark, N Engl J Med, 1999

Vasküler yatak normal bile olsa, vasküler yan yollar ve çalma ile doku hipoksisi kaçınılmaz

Growth Factor	Cell Source	Primary Action in Wound Healing
PDGF family		
PDGF	Platelets Fibroblasts Macrophages Vascular endothelial cells Vascular smooth muscle cells	• Chemotactically attracts fibroblasts, neutrophils, monocytes, and smooth muscle cells to the wound • Activates macrophages to release growth factors • Promotes fibroblast proliferation and production of extracellular matrix
VEGF	Platelets Fibroblasts Macrophages Keratinocytes	• Stimulates (lymph)angiogenesis • Enhances endothelial cell migration and proliferation
EGF family		
EGF	Platelets Fibroblasts Macrophages	• Stimulates the proliferation of keratinocytes, fibroblasts, vascular endothelial cells • Enhances the production of fibronectin
TGF-α	Platelets Macrophages Keratinocytes	• Similar to EGF • Induces angiogenesis
IGF family		
IGF	Fibroblasts Macrophages Neutrophils Hepatocytes	• Promotes re-epithelialization • Stimulates fibroblast proliferation
FGF family		
bFGF	Fibroblasts Macrophages Endothelial cells	• Acts as a mitogen for fibroblasts • Induces angiogenesis • Stimulates granulation tissue formation, matrix remodeling, and re-epithelialization
KGF	Fibroblasts	• Acts as a mitogen for epithelial cells
TGF-β family		
TGF-β1-3	Platelets Fibroblasts Macrophages Keratinocytes	• Acts as a potent chemoattractant for macrophages • Acts as a mitogen for fibroblasts • Stimulates or inhibits proliferation of various cells • Promotes granulation tissue formation and its tensile strength



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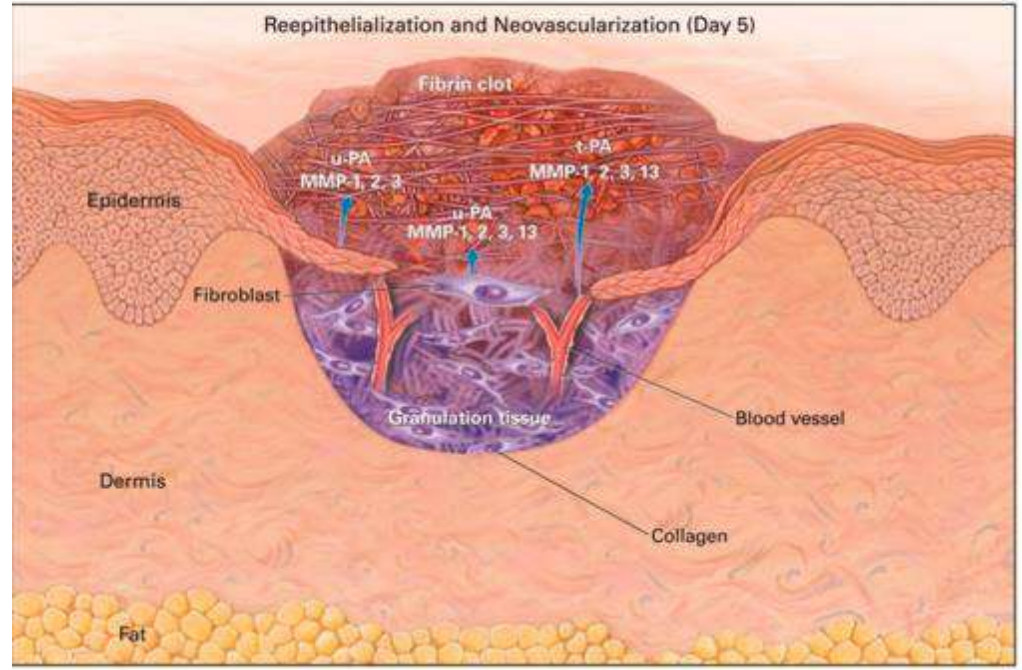


B

Patogenezde en önemli noktalardan biri

Diyabetik ayak yarası = doku büyüme faktörü eksikliği

İnsan Kaynaklı Rekombinant Epidermal Büyüme Faktörü

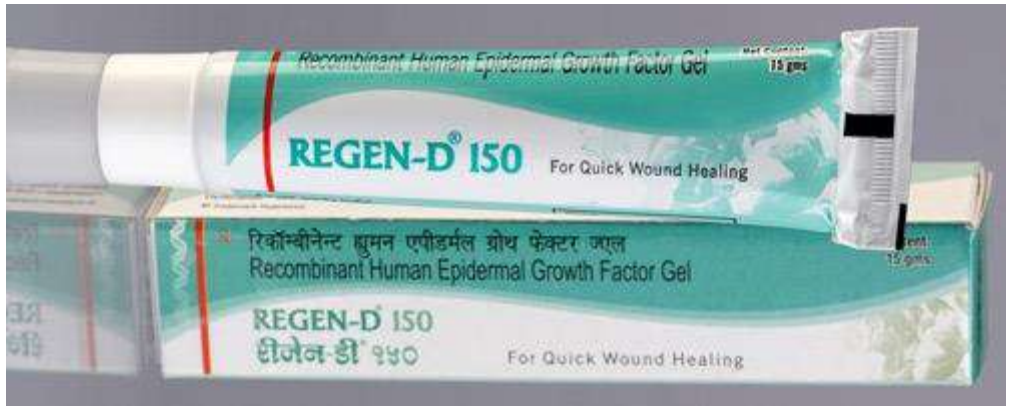
Epidermal büyüme faktörü (epidermal growth factor) ilk kez 1922 doğumlu, 1986 yılında Nobel fizyoloji veya tıp ödülünü almış olan Stanley Cohen tarafından bulunmuştur.

EGF evrim sırasında korunmuş eski bir polipeptid olup birçok hayvan türünde bulunur ve türler arasında benzerliği yüksek bir yapıya sahiptir. 53 amino asitten oluşan bir polipeptittir.

Vücutta hasar durumunda trombositlerden bol miktarda üretilir (diyabetik ayak ülserinde PRP uygulamasını hatırlayınız). Acil durumda hücre çoğalmasını sağlamak için vücut sıvılarında hazır halde de bulunur.

Kaynak- Heberprot-P tanıtım özetinden alınmıştır

Türkiye'deki tek topikal rhEGF 150



- Topikal jel
- Yüzeysel uygulama
- Günde iki kez

- Toz
- Jel
- Krem

Table 6. Application parameters of topical growth factors for skin wounds

Growth factor	Dosage form	Concentration	Common dose	Frequency	References
bFGF	Powder	Adjustable preparing solution	150 IU/cm^2 or 1 μg/cm^2	Once or twice per day	4–6,8,9,13,14,16,24,27
	Gel	2100 IU/g	150 IU/cm^2	Once per day	96–99
aFGF	Powder	Adjustable preparing solution, e.g. 1000 IU/mL	100 IU/cm^2	Once per day	42–43,45
EGF	Powder or solution	Adjustable preparing solution, e.g. 2000 IU/mL or 2.5 to 5.0 μg/mL or 10.0 μg/g	400 IU/cm^2 or 80 ng/cm^2	Once per day	21,100–103
	Gel or cream	10 μg/g or 20 to 40 μg/g	1 μg/cm^2 or 50 000 IU/cm^2 or 80 ng/cm^2	Once every 1–4 days	60,67,104–107
GM-CSF	Powder	Adjustable preparing solution	5 μg/cm^2	Once per day	108
	Gel	10 μg/g	1 μg/cm^2 or 10 μg/cm^2	Once per day	80–83,89
PDGF	Powder	Adjustable preparing solution, e.g. 100 μg/mL	10 μg/cm^2	Once per day	93
	Gel	10 μg/g	10 μg/cm^2	Once per day	90–92,94–95

bFGF basic fibroblast growth factor, *aFGF* acidic fibroblast growth factor, *EGF* epidermal growth factor, *GM-CSF* granulocyte macrophage colony stimulating growth factor, *PDGF* platelet-derived growth factor

- bFGF-basic fibroblast growth factor
- aFGF- acidic fibroblast growth factor
- GM-CSF
- PDGF- plateled derived growth factor

Chun-mao Han et all. Clinical guideline on topical growth factors for skin wounds. *Burns & Trauma,* 2020, 8, tkaa035

Table 3. Quality of evidence and Grading of Recommendations Assessment Development and Evaluation (GRADE) recommendations for topical application of epidermal growth factor in different types of wounds

Wound type	Quality of evidence	GRADE recommendation	References
Superficial partial-thickness burns	Moderate	Weak	47–59
Deep partial-thickness burns	Moderate	Weak	47–62
Donor sites	Moderate	Weak	47–51
Redisual granulation wounds after burns	Moderate	Weak	48,50,51,53
Diabetic foot ulcers	High	Strong	47,63–70
Venous ulcers	Moderate	Weak	71–73
CO_2 laser treated wounds	Moderate	Weak	74–76
Grafted wounds	Low	Weak	48
Chronic ulcers after burns	Low	Weak	48,53
Radiative dermatitis wounds	Low	Weak	77
Leg ulcers	Low	Weak	78

Aslında sadece diyabetik ayak ülserlerinde kanıt düzeyi yüksek bulunmuş ve kuvvetle kullanımı önerilmiş

Chun-mao Han et all. Clinical guideline on topical growth factors for skin wounds. *Burns & Trauma,* 2020, 8, tkaa035

Evaluation of the efficacy and safety of topical epidermal growth factor Regen-D® in diabetic foot wounds: a randomised, parallel group phase III study

Bulent M Ertugrul, Nur Yapar, Meltem Taşbakan, Arife Polat Duzgun, Emre Ozker, Şamil Aktaş, Başar Kaya, Murat Ilkar Gelisen, Volkan Öztuna, Işık Şenkaya Sığnak and Mevlüt Türe

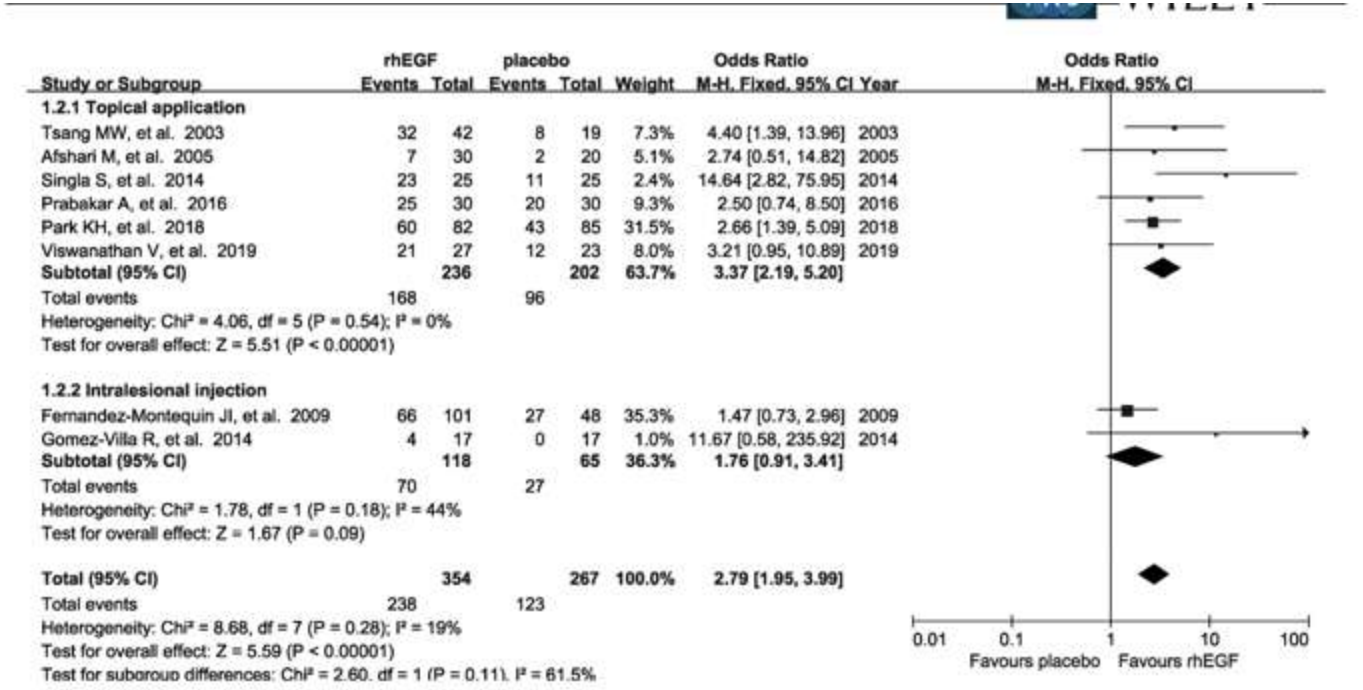
- Çalışma grubu 76 vs kontrol 66 (standart tedavi)…G1, 2…
- 1. Ay'dan itibaren etki başlamış…
- İlk ayda; kapanma 2 kat yüksek, granülasyon aynı…
- İkinci ayda; istatistiksel anlamlı fark yok,
- Dördüncü ayda- çalışma sonunda; kapanma 2 kat yüksek…
- Çalışma sonunda; yanıtsız çalışma grubunda 9 kat daha az….
- Rekürrens çalışma grubunda hiç yok- 10 ay izlem…

Table 2. Results of patient evaluations.

Month 1 evaluation	**Control group (*n*=66)**	**Study group (*n*=76)**	***P*-value**
No granulation	5 (7.6)	1 (1.3)	0.152
Existence of granulation	55 (83.3)	60 (80.0)	0.774
Wound closure	6 (9.1)	14 (18.7)	0.165
Month 2 evaluation	**Control group (*n*=50)**	**Study group (*n*=63)**	***P*-value**
No granulation	4 (8.0)	4 (6.3)	0.984
Existence of granulation	28 (56.0)	30 (47.6)	0.485
Wound closure	18 (36.0)	29 (46.0)	0.379
Month 4 evaluation	**Control group (*n*=56)**	**Study group (*n*=60)**	***P*-value**
No granulation	7 (12.5)	2 (3.3)	0.064
Existence of granulation	32 (57.1)	19 (31.7)	<0.001
Wound closure	17 (30.4)	39 (65.0)	0.006
End of study evaluation	**Control group (*n*=69)**	**Study group (*n*=76)**	***P*-value**
Wound	31 (44.9)	20 (26.3)	0.019
Wound closure	27 (39.1)	55 (72.4)	<0.001
No response	9 (13.0)	1 (1.3)	0.005
Recurrence	2 (2.9)	0 (0.0)	0.136

Gerçek yaşam verisi?

- Sistematik derleme…RCT…
- rhEGF vs placebo…
- PRİSMA sensitivite analizini geçen 9 çalışma,
- 720 katılımcı (404 çalışma, 316 placebo)
- 6 tane topikal uygulama
- 2 tane intralezyoner uygulama
- 1 bias nedeniyle değerlendirme dışı



rhEGF'ün gerek topikal, gerekse intralezyoner uygulaması iyileşmeyi olumlu etkiliyor…

Ding-Yun Zhao et all. Efficacy and safety of recombinant human epidermal growth factor for diabetic foot ulcers: A systematic review and meta-analysis of randomised controlled trials. Int Wound J. 2020;17:1062–1073.

Topikal vs İntralezyoner?

Meta-Analysis > Ann Vasc Surg. 2020 Jan;62:442-451. doi: 10.1016/j.avsg.2019.05.041. Epub 2019 Aug 5.

Topical Recombinant Human Epidermal Growth Factor for Diabetic Foot Ulcers: A Meta-Analysis of Randomized Controlled Clinical Trials

Qi Yang [1], Yonghong Zhang [2], Haiyang Yin [1], Yanjun Lu [1]

- Derleme, RCT
- 7 adet…610 katılımcı…
- Kıyaslama çalışması yok,
- Enfeksiyon kontrol altında,
- Osteomyelit olmamalı,
- Topikal Wagner G1,2 (RR, 1.61; 95% CI, 1.32 to 1.97; I^2 = 0%)
- İntralezyonel daha derin ülserde etkili (RR, 2.06, 95%, CI 0.35 to 12.22; I^2 = 50%).

Topikal = G1,2
İntralezyoner >2

1. Güvenlik verisi yetersizliği nedeniyle çocuk, hamile, emzirenler, >65 yaş uygulanması önerilmez,
2. Debridman sonrası ve enfekte olmayan yaraya uygulanması önerilir,
3. Ciddi periferik enflamasyon durumunda uygulanması önerilmez,
4. Şimdiki verilere göre en iyi etkiyi 100-1000IU/cm2'de görülür,
5. Doz sıklığı; günde birden fazla olmalıdır,
6. Toplam süre yara yatağı graftlemeye hazır oluncaya kadar kullanılabilir,
7. Farklı EGF'lerin bir arada kullanımı ile ilgili iyi sonuçlar olsa da ileri çalışmalara ihtiyaç vardır,
8. EGF ile vakum kapama ve aljinat kombinasyonu iyi sonuçlar verdiğine dair çalışmalara olsa da yeni verilere ihtiyaç vardır,
9. EGF etkisini azaltan; etanol, hidrojen peroksid, gümüş ile kombinasyon yapılmamalıdır,
10. Uygulama bölgesinde ciltte kanser şüphesi durumunda uygulanmamalıdır,

Guideline

Clinical guideline on topical growth factors for skin wounds

Chun-mao Han[1,*], Biao Cheng[2], Pan Wu[1] and writing group of growth factor guideline on behalf of Chinese Burn Association

[1]Department of Burns & Wound Care Center, the Second Affiliated Hospital of Zhejiang University School of Medicine, No. 88 Jiefang Road, Hangzhou 310009, China and [2]Department of Burns & Plastic Surgery, General Hospital of Southern Theater Command, PLA, No. 111 Liuhua Road, Guangzhou 510000, China

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Genel sonuç…G3,4 maliyet etkin

Sadece DM ayak pratiğinde mi? Etkin….

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2019, VOL. 30, NO. 1, 96–101
https://doi.org/10.1080/09546634.2018.1468546

Taylor & Francis
Taylor & Francis Group

SHORT REPORT

Human recombinant epidermal growth factor in skin lesions: 77 cases in EPItelizando project

Jordi Esquirol-Caussa[a,b] and Elisabeth Herrero-Vila[a,c]

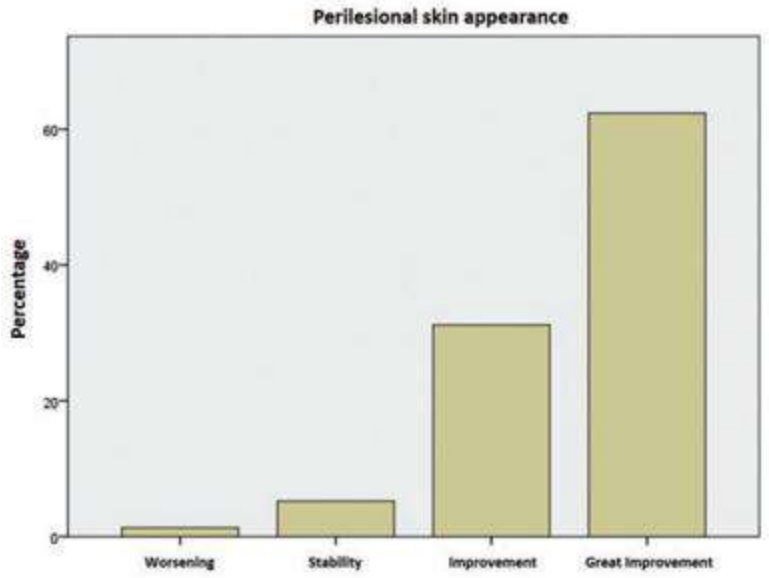
[a]Centro Médico Teknon, Barcelona, Spain; [b]Servei Universitari de Recerca en Fisioteràpia (SURF), Escoles Universitàries Gimbernat (adscrites a la Universitat Autònoma de Barcelona), Barcelona, Spain; [c]Servei de Medicina Preventiva, Àptima, Terrassa, Barcelona, Spain

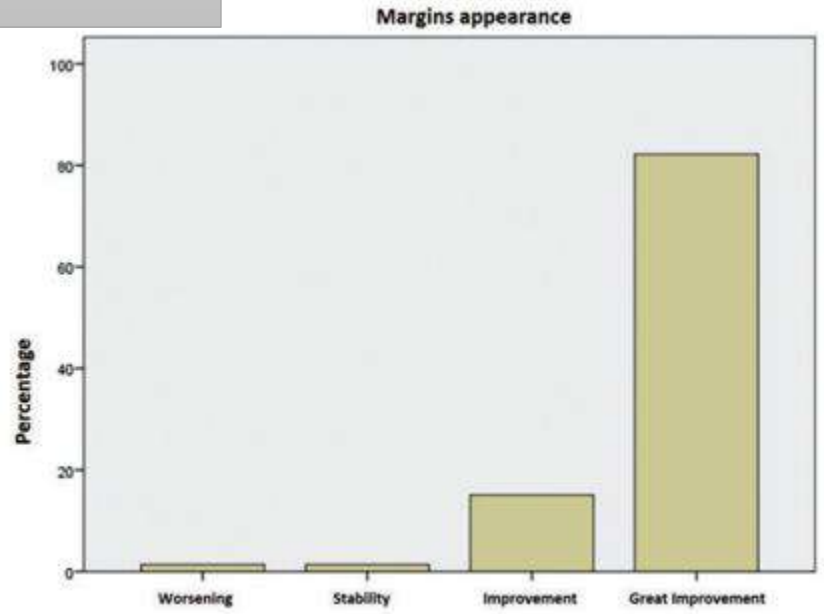
Epitelizasyon ve iyileşme

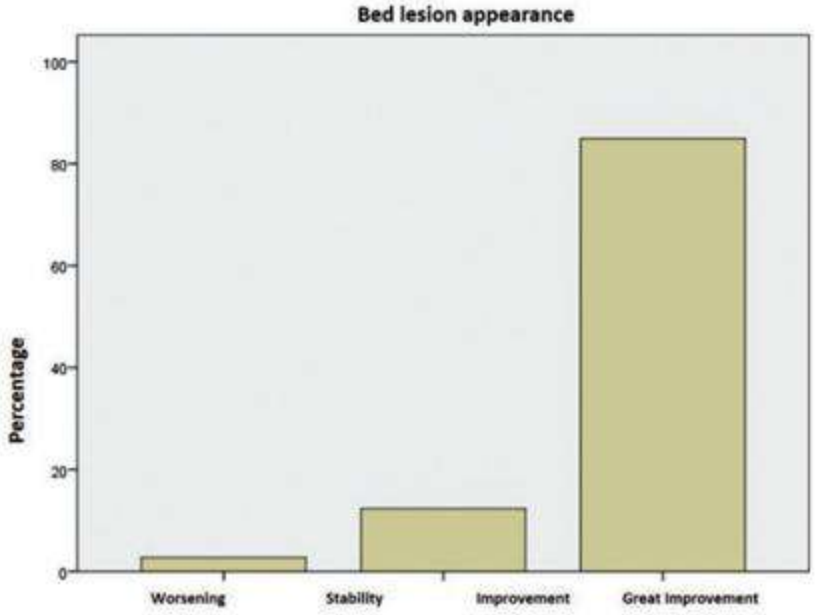
- Yara etrafında %60
- Yara sınırlarında %80
- Yara yatağında %80

Table 3. Percentage of ulcers with higher and lower than 40% healing rate in 4 weeks.

	% of healing in 4 weeks	
	<40% healing in 4 weeks *N* (%)	>40% healing in 4 weeks *N* (%)
Venous ulcer	17 (56.66)	13 (43.33)
Pressure ulcer	6 (75)	2 (25)
Diabetic foot	2 (28.57)	5 (71.43)
Posttraumatic ulcer	2 (33.33)	4 (66.66)
Vasculitis	2 (100)	–
Arterial ulcer	–	1 (100)
Hypertensive ulcer	1 (100)	–
Postgraft ulcer	1 (100)	–
Total	31 (55.36)	25 (44.64)







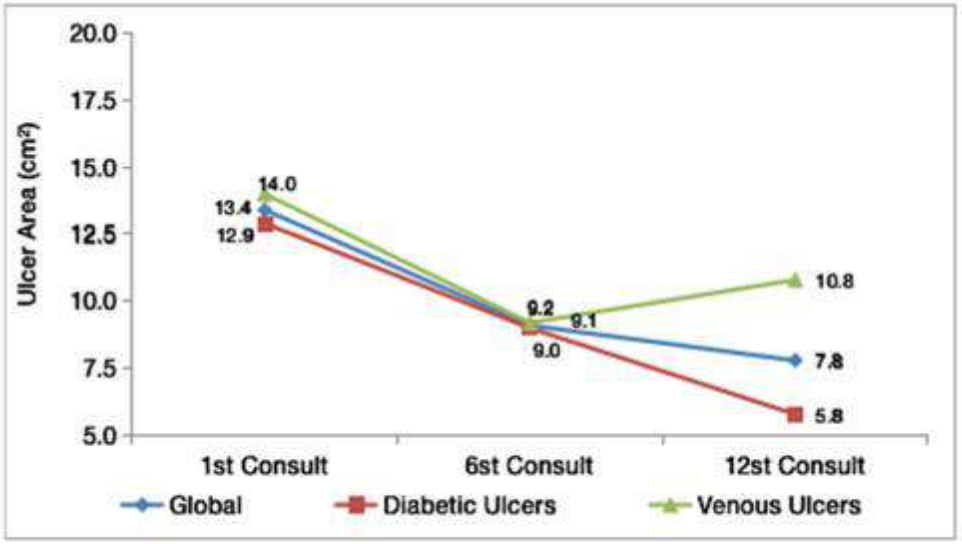
Article

rhEGF-Loaded Hydrogel in the Treatment of Chronic Wounds in Patients with Diabetes: Clinical Cases

Beatriz Guitton Renaud Baptista de Oliveira [1], Bianca Campos Oliveira [1,*], Gabriela Deutsch [2], Fernanda Soares Pessanha [3], Rossana Mara da Silva Moreira Thiré [4] and Selma Rodrigues de Castilho [2]

- Eksüdasyona etkisi?
- İyileşmeye etkisi?

- Toplam 10 hasta
- 12 hafta takip
- En hızlı düzelme venöz ülserlerde
- Eksüdasyonda ciddi azalma %20…Azalma olmayan yok



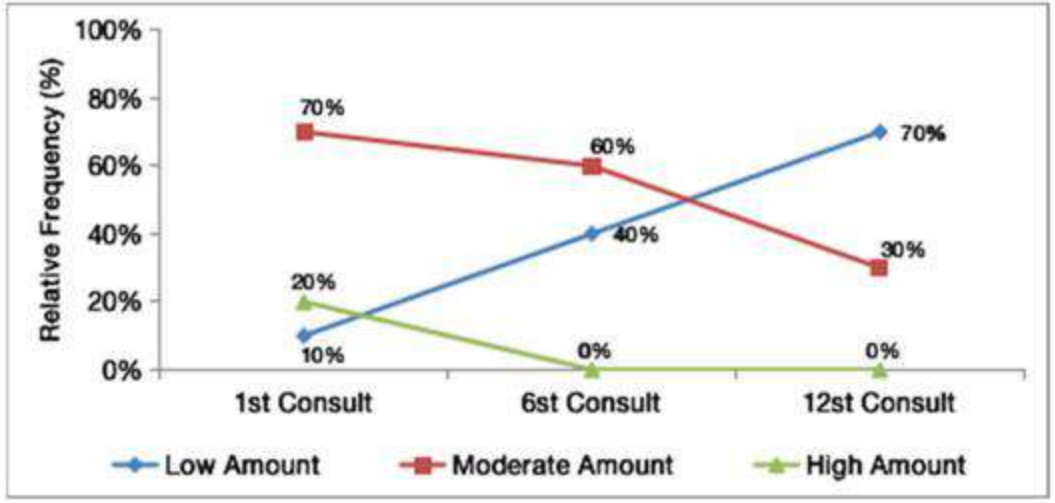


Figure 1. The evolution of the mean area of the lesion in the three evaluations.

RKÇ'larda Regen D'nin yeri?

Review Article

The Role of Recombinant Proteins and Growth Factors in the Management of Diabetic Foot Ulcers: A Systematic Review of Randomized Controlled Trials

Elahe Mahdipour[1] and Amirhossein Sahebkar[2,3,4,5]

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TABLE 4: Outcomes of RCTs that evaluated EGF safety and effectiveness.

Ref	Type of growth factor	Wound closure	Mean time to heal in treatment groups	Mechanism mentioned as complete healing		Confounders				Further outcomes	
				Granulation tissue	Reepithelialization	Sex	Baseline HbA1c	Wound size	Offloading	Recurrence rate	Amputation rate
[16]	EGF	More complete healing in the rhEGF group ($p = 0.033$); decreased in area size ($p = 0.049$); and more epithelial islands in the wound bed were present ($p = 0.025$)	8 weeks	Y	Y	NM	NM	NM	NM	NM	NM
[17]	EGF	Granulation tissue covering ≥50% of the ulcer at 2 weeks was achieved by more cases in the EGF groups ($p = 0 \cdot 000015$). Shorter time to complete healing in the 75 μg group ($p = 0.006$)	3 weeks	Y	NM	NM	NM	NM	NM	2 cases in the placebo group	29 cases in all groups
[18]	EGF	Reduced seropurulent discharge in the EGF group $p = 0.0495$ and serous discharge $p = 0.009$. More granulation tissue $p = 0.041$. More complete healing in the EGF group $p = 0.007$	17.2 ± 1.3 ($p = 0.01$)	Y	NM	NM	NM	NM	NM	NM	NM
[19]	EGF	More cases with complete healing in the 0.04% hEGF group. Patients in the 0.04% hEGF group also healed more quickly than those in the other groups ($p = 0.0003$). No significant difference in healing time between the 0.02% hEGF and control groups	6 weeks in the 0.04% hEGF group ($p = 0.0003$)	Y	Y	N	NM	NM	NM	NM	2 cases in placebo and 2 in 0.02% hEGF groups
[20]	EGF, REGEN-D150	For wounds >6 cm^2 in size treatment resulted in more healing ($p < 0.002$). A reduced healing time in the EGF group. At the end of 10 weeks, 69% of wounds healed versus 21% in placebo control	9 weeks	Y	Y	NM	NM	NM	NM	NM	NM

EGF: epidermal growth factor; Y: yes; N: no; NM: not mentioned.

- >6 cm^2 yaralarda daha etkili
- İyileşme süresinde kısalma anlamlı
- 10. Hafta sonunda %69 kapanma

rEGF gelecekteki uygulanma alanları-1

Skar tedavisinde vaka bazında etkin…

The Efficacy and Safety of Epidermal Growth Factor Combined with Fractional Carbon Dioxide Laser for Acne Scar Treatment: A Split-Face Trial

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J Clin Aesthet Dermatol. 2022;15(7):44-48.

BACKGROUND: Epidermal growth factor (EGF) stimulates collagen production and supports the wound healing process. However, there are no studies on fractional carbon dioxide (CO_2) laser combined with EGF for acne scar treatment. **OBJECTIVE:** We sought to evaluate the efficacy and safety of fractional CO_2 laser combined with topical EGF versus fractional CO_2 laser alone in the treatment of acne scars. **METHODS:** Twenty-three patients with atrophic acne scars underwent three monthly sessions of randomized split-face application of fractional CO_2 laser combined with topical EGF or placebo twice daily for seven days following each laser session. Scar improvement was evaluated at one month and three months posttreatment by two blinded dermatologists and the Antera 3D® skin analysis system. Wound healing response and adverse events were also evaluated. **RESULTS:** Twenty-one patients completed the trial. According to dermatologist grading and skin analysis system, EGF showed significant superiority at three months posttreatment compared to placebo. The wound healing response did not differ between the groups. Surprisingly, the melanin index on the EGF side showed a significant decrease at three months posttreatment, compared to placebo. There was no allergic reaction to the topical EGF. **CONCLUSION:** Treatment with topical EGF after ablative fractional CO_2 laser improves the clinical appearance of atrophic acne scars, and EGF may help decrease skin pigmentation after laser treatment. The use of topical EGF is safe when applied to post-laser ablation. **KEYWORDS:** Epidermal growth factor, fractional carbon dioxide laser, acne scar

TABLE 1. Evaluation of scar improvement by physician and Antera 3D® system

TIME	QUARTILE GRADING SCALE BY PHYSICIAN MEAN±SD		*P*-VALUE (BETWEEN GROUPS)	PERCENTAGE OF IMPROVEMENT BY ANTERA 3D® SYSTEM MEAN±SD		*P*-VALUE (BETWEEN GROUPS)
	EPIDERMAL GROWTH FACTOR	PLACEBO		EPIDERMAL GROWTH FACTOR	PLACEBO	
1 month posttreatment	1.71±0.56	1.67±0.58	0.31	18.97±8.60	15.95±9.97	0.11
3 months posttreatment	2.76±0.54	2.57±0.51	0.04	27.40±10.50	21.28±10.50	0.01

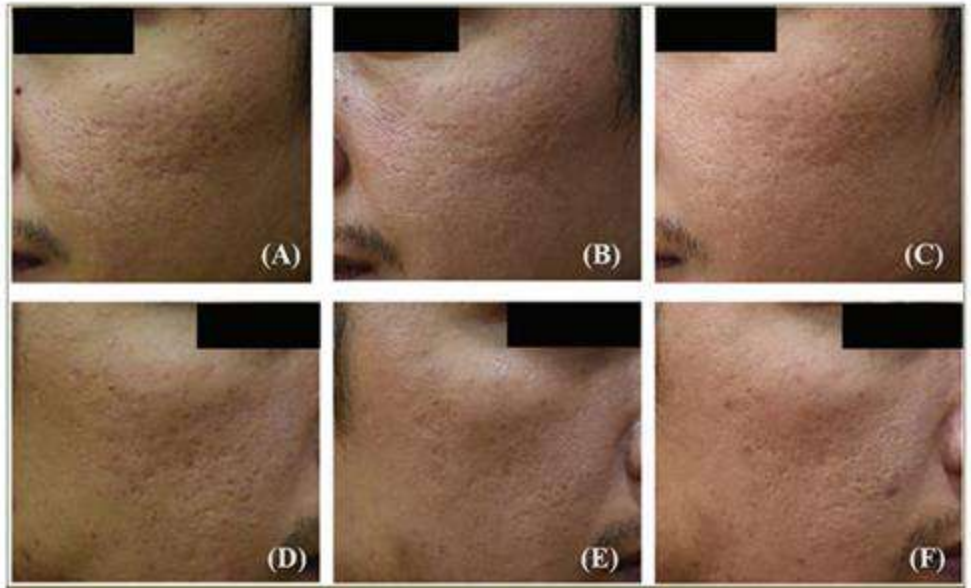

FIGURE 1. Clinical photographs of 29-year-old male; Figures 1A–1C show the side treated with the epidermal growth factor, and Figures 1D–1F show the placebo-treated side. (A) and (D) are baseline. (B) and (E) are at one month posttreatment. (C) and (F) are at three months posttreatment.

rEGF gelecekteki uygulanma alanları-2

- Atopik dermatitis…
- Deney haycanı- kulak modeli
- Enflamasyon çözülüyor
- Cilt kalınlığı artıyor
- Etki hızlı ortaya çıkıyor…

Sonuç- molekül yeniden konumlandırılmaya uygun….

OPEN

Topical administration of EGF suppresses immune response and protects skin barrier in DNCB-induced atopic dermatitis in NC/Nga mice

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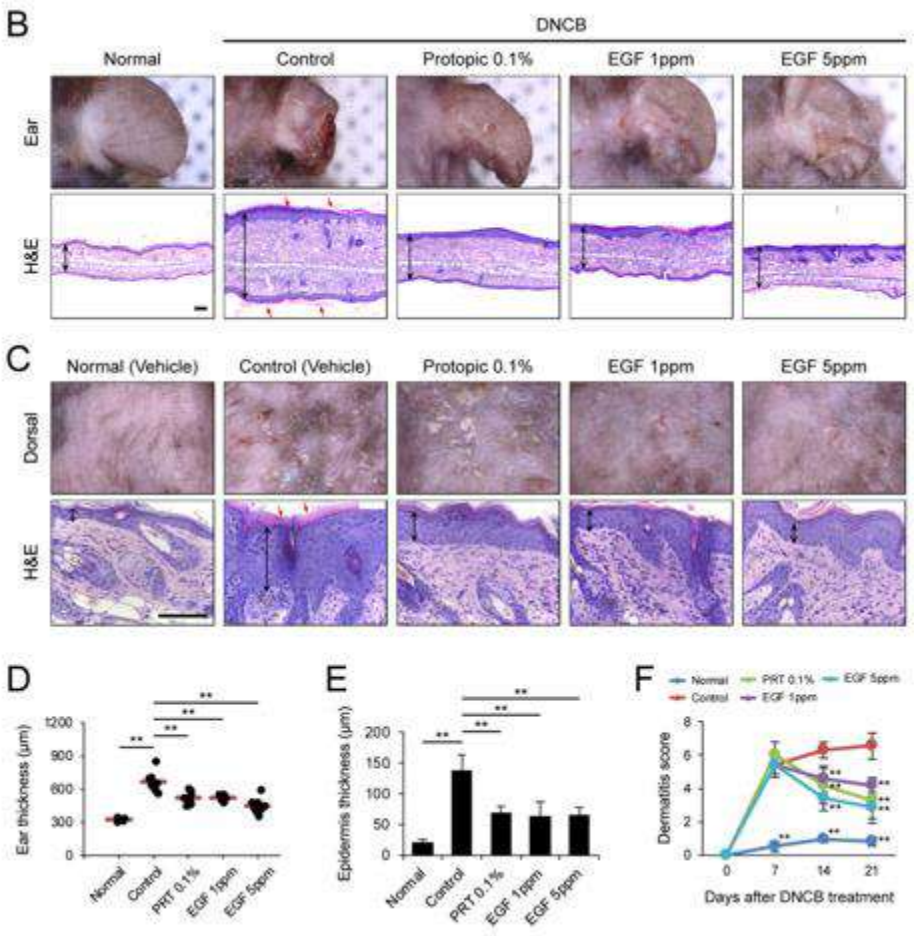
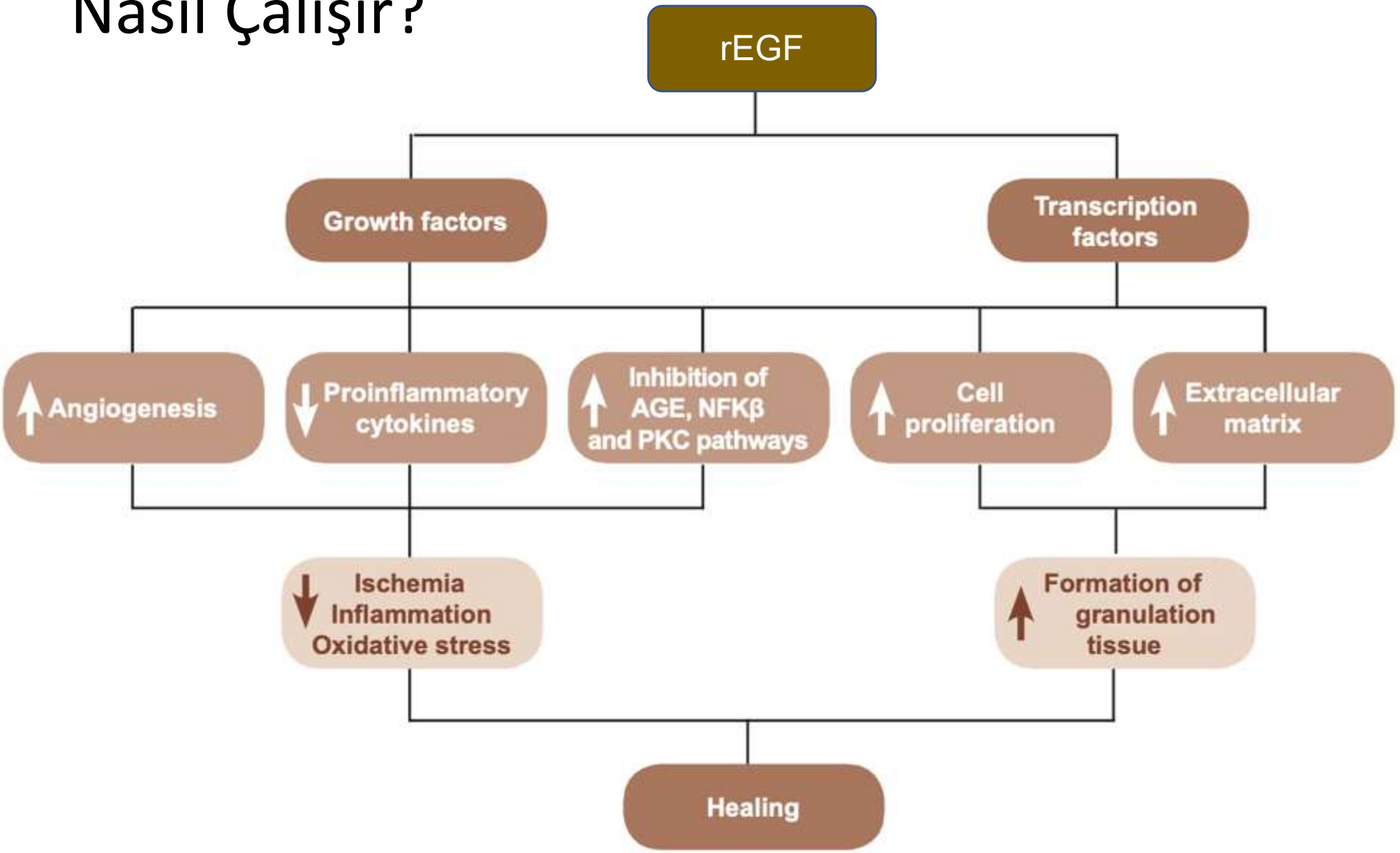
Young-Je Kim[1], Mi Ji Choi[1,2], Dong-Ho Bak[1,2], Byung Chul Lee[1,2], Eun Jung Ko[3], Ga Ram Ahn[1], Seung Won Ahn[4], Moo Joong Kim[5], Jungtae Na[1] & Beom Joon Kim[1,2]



y skin disease characterized by a complex, er dysfunction, immunology, and pruritus. Although thelial homeostasis and wound healing, the effect a new therapy for AD, the anti-AD potential of EGF in NC/Nga mice using 2,4-dinitrochlorobenzene to evaluate its therapeutic effect on DNCB-induced ar thickness, epidermal hyperplasia, serum total er loss in NC/Nga mice with DNCB-induced AD. In ich as filaggrin, involucrin, loricrin, occludin, and treatment. These beneficial effects of EGF on AD may ated cytokines, mast cell hyperplasia, and protease lymphopoietin (TSLP), which are triggers of AD. Taken entially protect against AD lesional skin via regulation

Nasıl Çalışır?



Hanlet Camacho-Rodríguez et al. Heberprot-P's Effect on Gene Expression in Healing Diabetic Foot Ulcers

Sonuçta…

Anjiyogenesis ↑

ANGPT1
(Angiopoietin 1)

Enflamasyon ↓

IL-1A
TNF alfa

No.	Gene	Fold change	P-value	Direction of change*
1	AGER	−1.20	0.190	
2	ANGPT1	1.45	0.001	↑
3	CDK4	1.48	0.009	↑
4	CDKN1B	1.04	0.568	
5	COL1A1	1.67	0.005	↑
6	CTGF	−1.28	0.302	
7	FOS	1.10	0.740	
8	HIF1A	−1.25	0.088	
9	IGFBP3	1.28	0.220	
10	IL17A	−2.17	0.079	
11	IL-1A	−13.70	0.000	↓
12	IL-6	−1.78	0.207	
13	MMP2	2.21	0.000	↑
14	MMP7	1.07	0.886	
15	MMP9	1.69	0.090	
16	NFKB1	-1.37	0.002	↓
17	P21	1.54	0.009	↑
18	PDGFB	1.68	0.002	↑
19	PHB	−1.20	0.073	
20	PLCG1	−1.08	0.325	
21	TGFB1	−1.08	0.540	
22	TIMP1	1.08	0.652	
23	TIMP2	1.43	0.007	↑
24	TNFA	−1.96	0.001	↓
25	TP53	1.99	0.000	↑
26	VEGFA	1.38	0.227	

Kollajen sentezi ↑
Extra sellüler matrix ↑

COL1A1
(collagen type I alpha 1 chain)

Myelofibroblast ↑

MMP2
(matrix metalloproteinase 2

TIMP2
(Tissue inhibitor of metalloproteinases 2

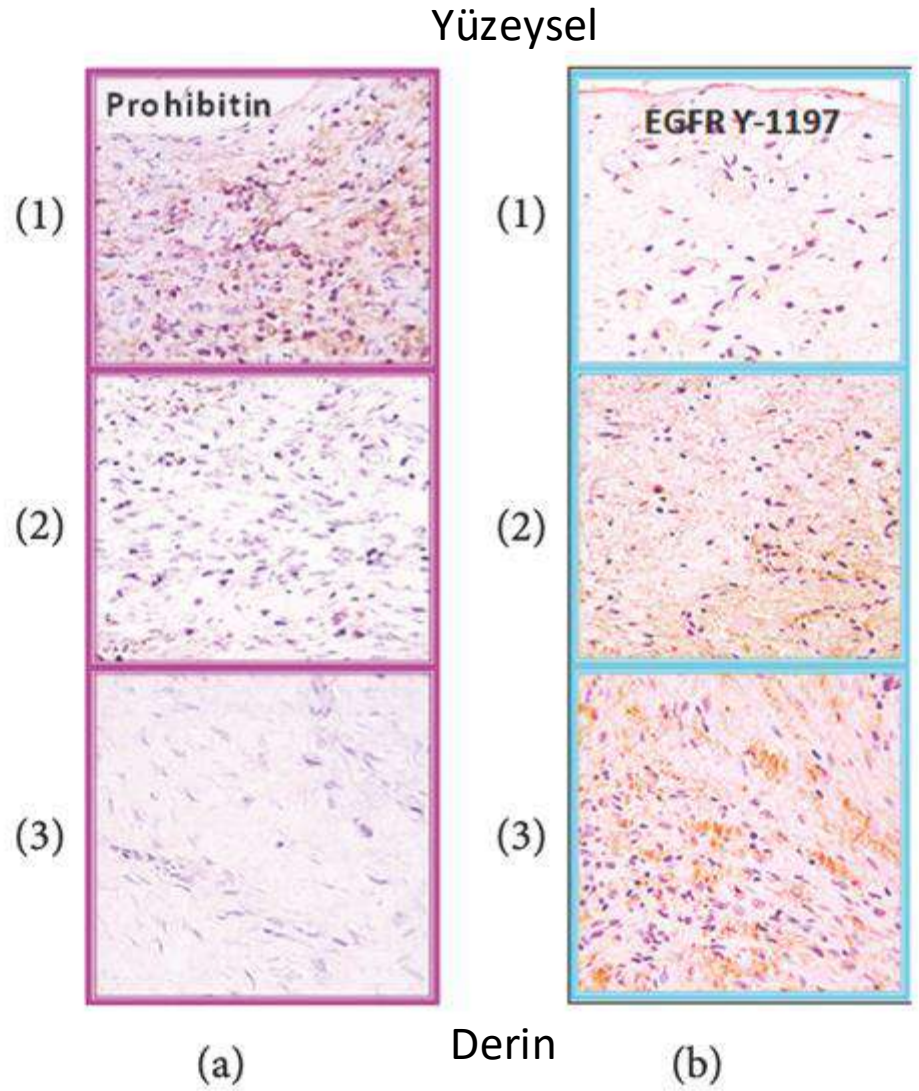
Epitelizasyon ↑

PDGFB
(Platelet Derived Growth Factor Subunit B)

Hanlet Camacho-Rodríguez et al. Heberprot-P's Effect on Gene Expression in Healing Diabetic Foot Ulcers

Prohibitin

- Aslında lipid dokuda yüksek oranda bulunur,
- Kronik ülserde; yüzeyde daha çok, derin dokuda daha az,
- Hücre siklüsü bloklajı; antimitojenik faktör
- EGF uygulandığında prohibitin doku dağılımı derine iniyor…
- Hücre siklüsünün başladığının indirekt göstergesi…

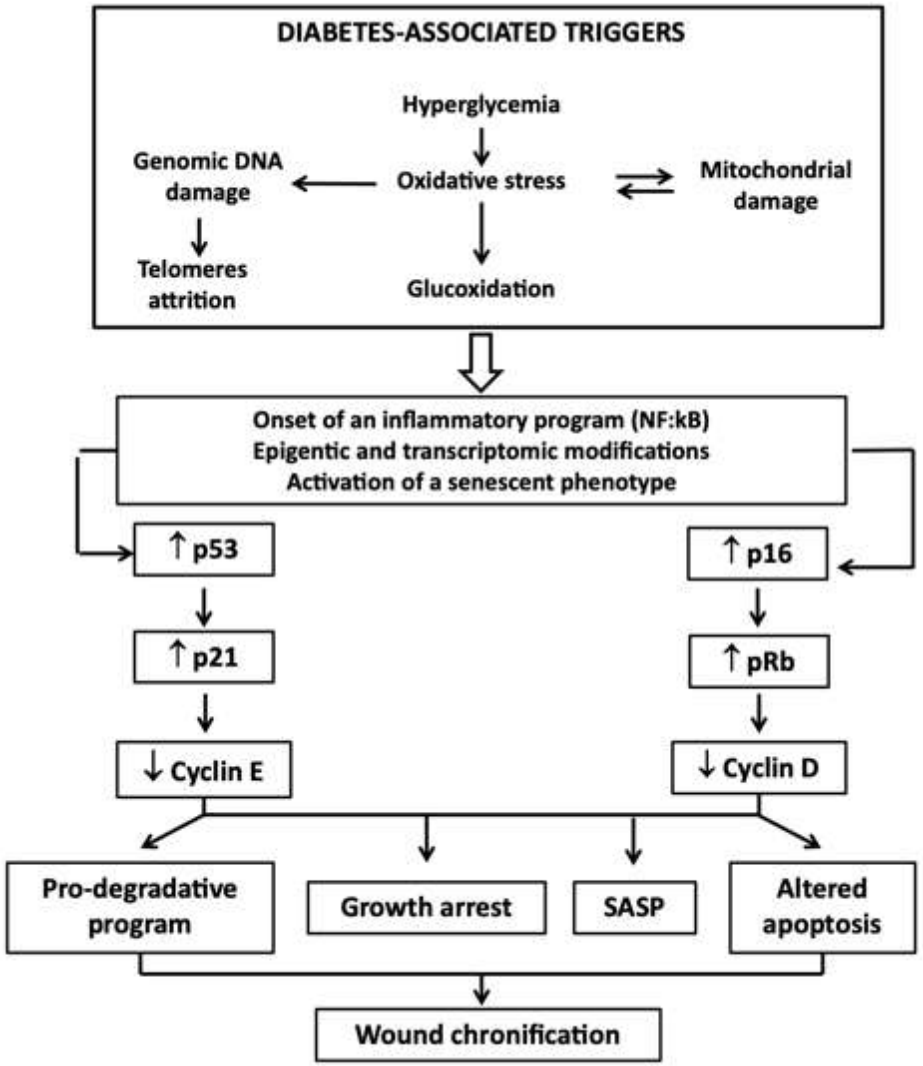


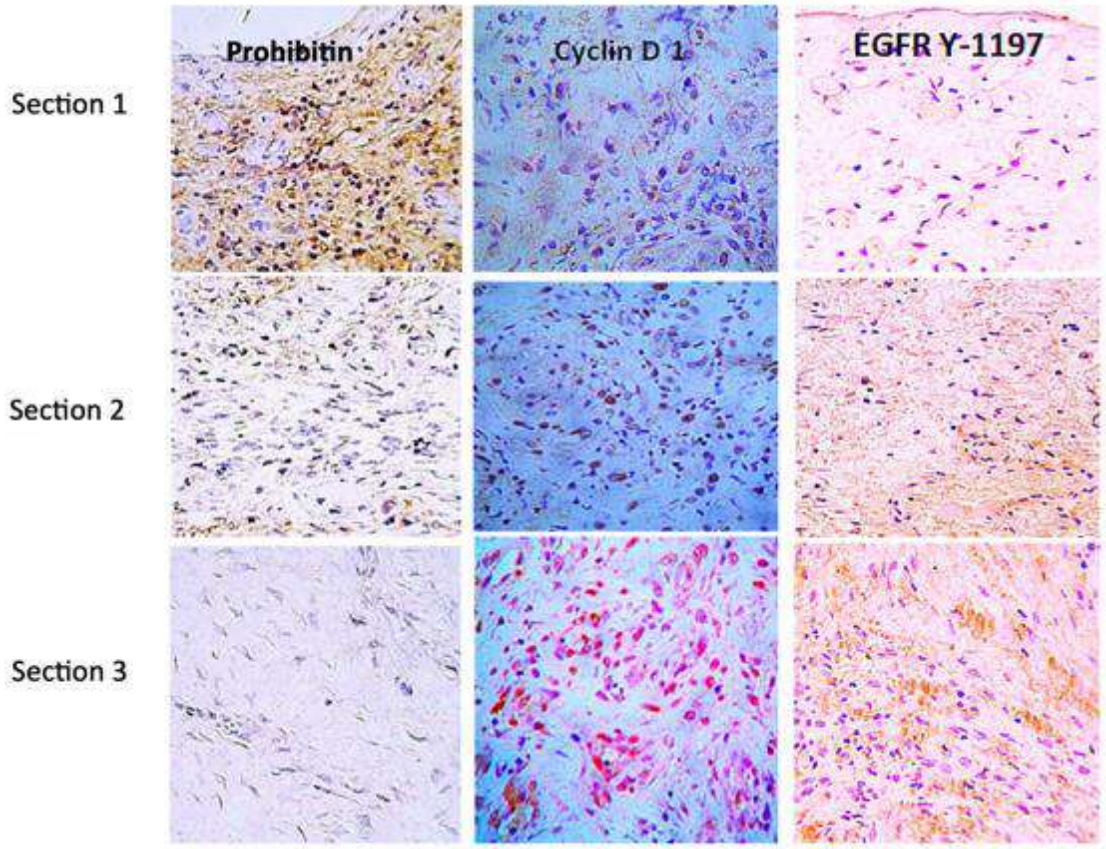
Peroksidaz boyası- prohibitin EGF sonrası her tabakaya yayılmış

2-6 mm cilt biyopsileri

Berlanga-Acosta J. Diabetic lower extremity wounds: the rationale for growth factors-based infiltration treatment. Int Wound J 2011; 8:612–620

Cyclin D-azalması





rhEGF uygulaması sonrası Cyclin D artışı ile hücre proliferasyonu artar

Jorge Berlanga-Acosta et all. Epidermal Growth Factor (EGF) intralesional infiltrations: From the bench to the diabetic ulcers cells

Integr Mol Med, 2019 doi: 10.15761/IMM.1000354 Volume 6: 1-7

Uygulama sonrası moleküler düzeyde ne oluyor?

- İlk 15 dk'da: EGFR'ü membran ekspresyonu artıyor,
- rhEGF endositoz ile hücre içine giriyor,
- 15 dk-24 saat: stoplazmik translokasyon ve endoplazmik organellerin dağılımı,
- 45dk-24 saat: nükleer translokasyon ve DNA'ya bağlanma,
- 24.saatten sonra:

-Hücre proliferasyonu,

-EGFR mitokondriyal birikmesi,

-rhEGF kollajene bağlanması ve ekstasellüler matriks sentezi

V.FalconCama,M.Fernandez Mayola,Y.Mendoza-Maŕıetal., "Epidermal growth factor based therapy promotes intracellular trafficking and accumulation of its receptor in the nucleus of fibroblasts from diabetic foot ulcers," *Journal of Diabetic Complications & Medicine*, vol. 01, no. 03, 2016.

Sıfır noktası- rhEGF ilk dakikası

- Fibroblast benzeri hücre membranı stabil
- ER'da değişim yok…

A

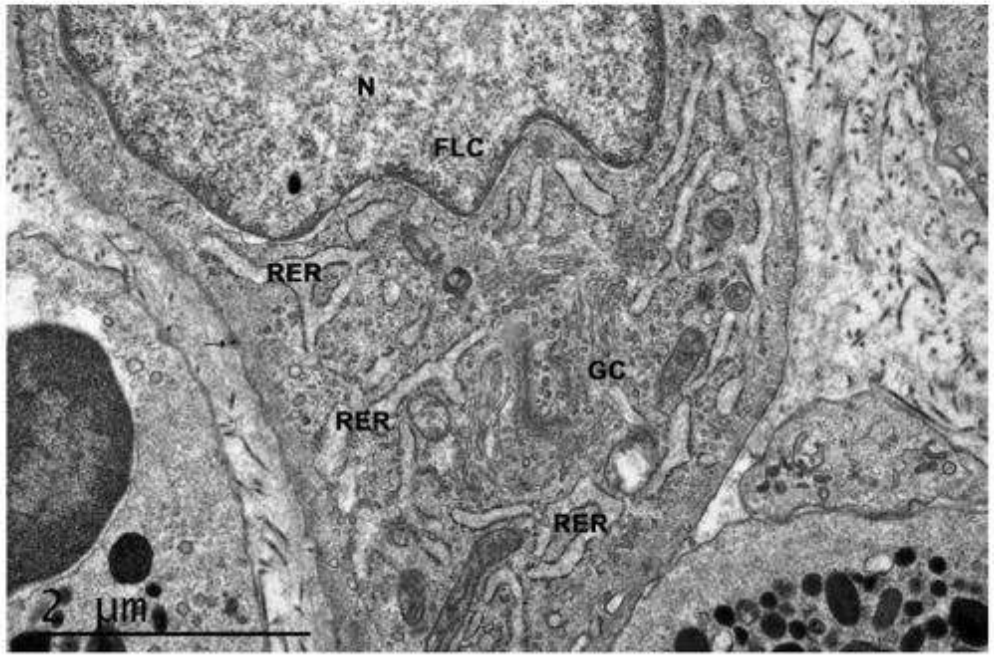


Figure 1A: Time Zero (T0) harvesting corresponds to the sample obtained minutes prior to the initial EGF infiltration. The image shows a negligible immunostaining on the plasma membrane of a Fibroblast-like cell (arrow). Rough endoplasmic reticulum (RER); Nucleus (N); Golgi complex (GC); fibroblast-like cell (FLC) (Bar=2 um).

45 dk sonrası-

- ER'da şişme,
- EGFR expresyonu (Vesikül)
- Fibroblast benzeri hücre membranında genişleme
- Kollajen matrix ve kollajen fiberde toplanma

B

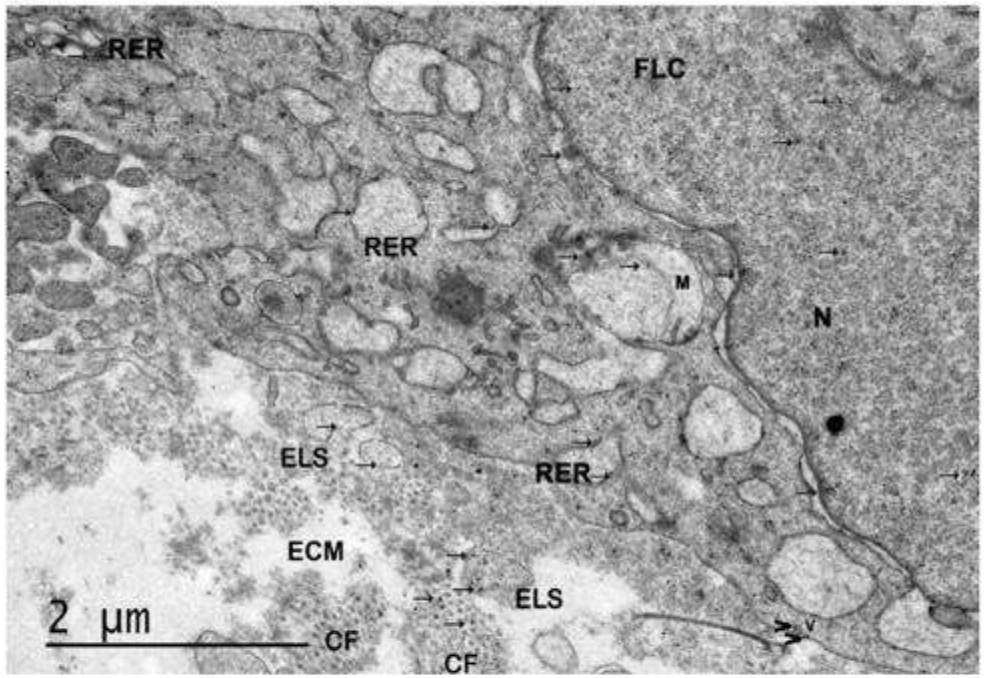
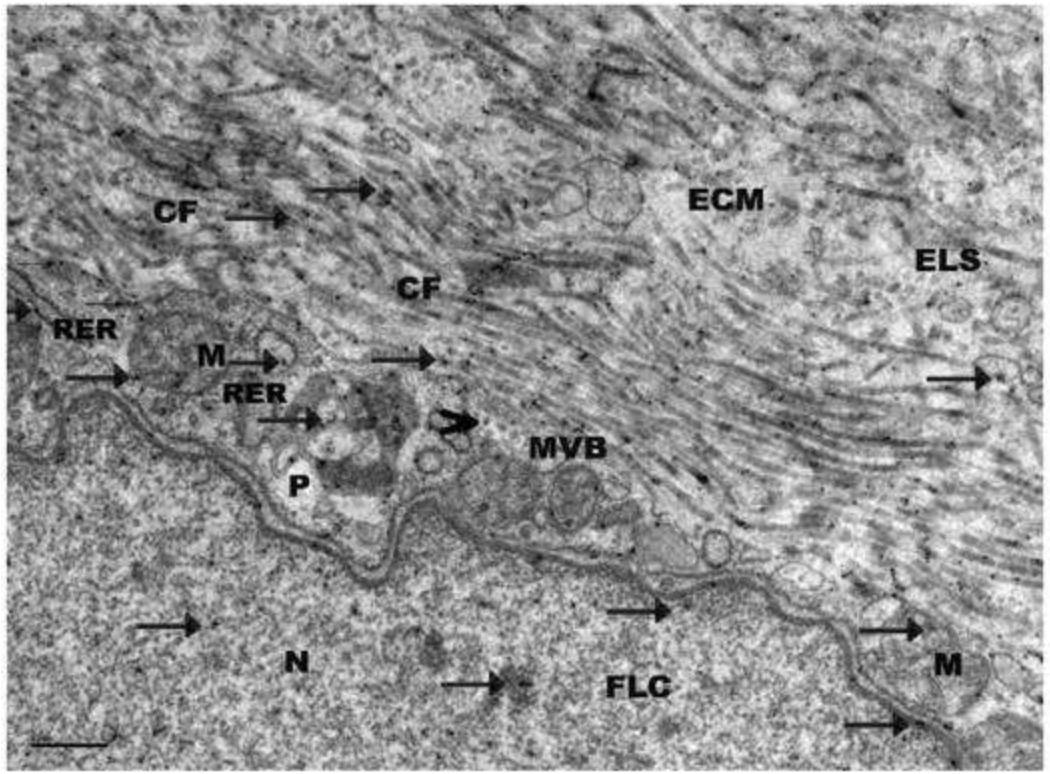


Figure 1B: Immunolabeling of EGFR (arrows) in part of a Fibroblast-like cell (FLC) from a biopsy sample obtained 45 minutes after EGF infiltration. Immunostaining appeared in mitochondria, RER and nucleus. Also note that EGFR was immunolabeled in vesicles (V) (arrowhead), on plasma membrane (arrowhead), the extracellular matrix (ECM), on collagen-like fibers (CF) and exosome-like structures (ELS) (Bar=2 um).

6 saat sonra-

- EGRF (oklar ile işaretli) yaygınlaşma ve hücre yüzeyine yayılma
- Kollajen fibrillerde çaprazlaşma ve yaygınlaşma
- MVB- multivesicular body; stoplazma içinde artar (sayıca + ebat)



24 saat sonra-

- Nükleus entegrasyonu
- rhEGF mitokondriyal birikme,
- rhEGF kollajene bağlanma, ekstrasellüler matriks sentezi

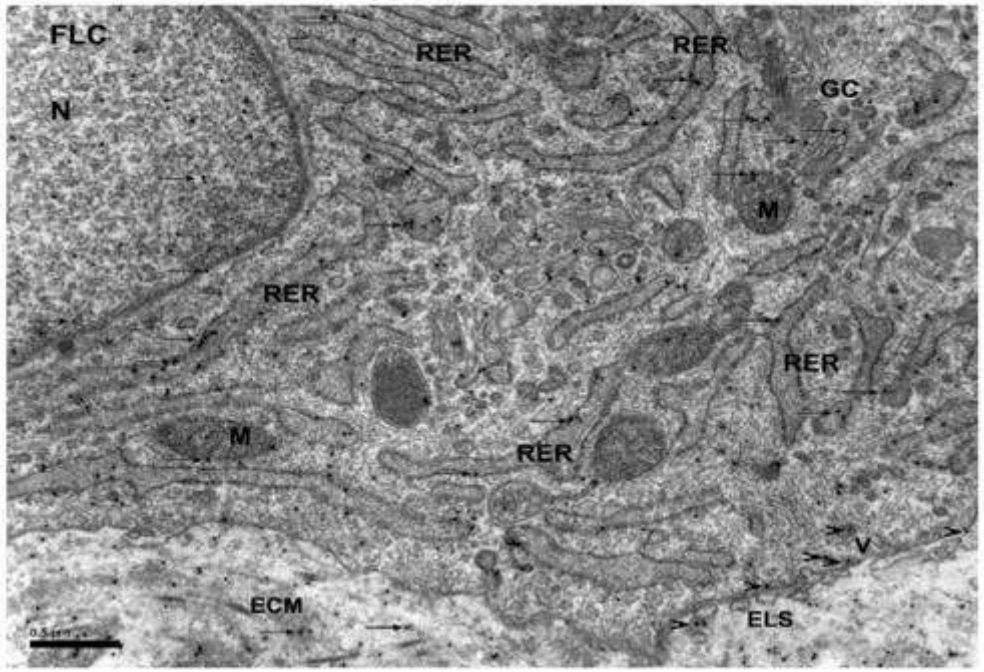


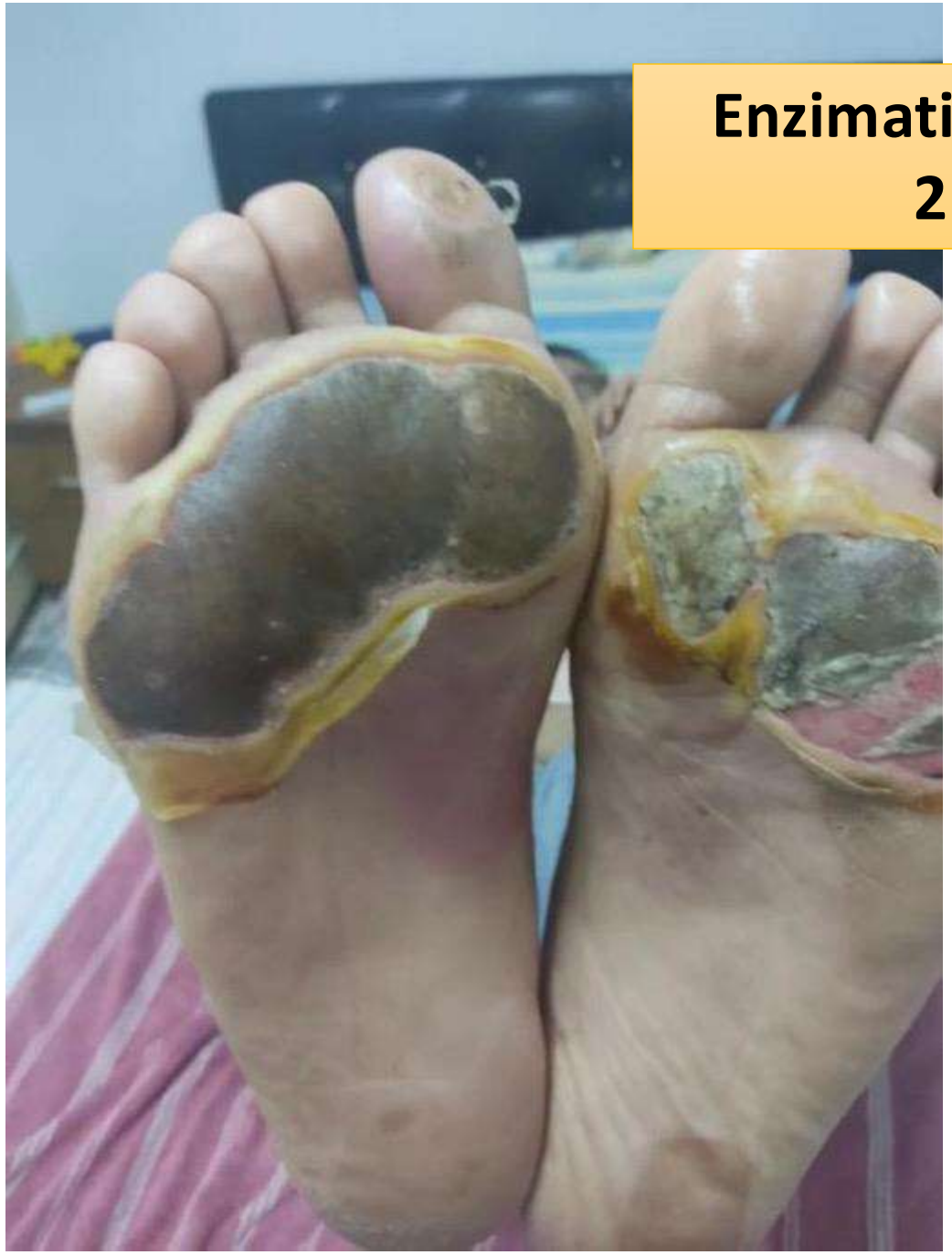
Figure 2D: Immunolabeling of PCNA in part of a fibroblast-like cell (FLC) from a biopsy of samples infiltrated with EGF at T24. Large labeling of RER, Golgi complex (GC) and mitochondria (M) were observed. Immunostaining of PCNA was also detected in nucleus (N), and extracellular matrix (ECM) (arrows). Also note immunostaining in plasma membrane, vesicles and exosome-like structures (ELS) (arrowheads) (Bar=0.5um).

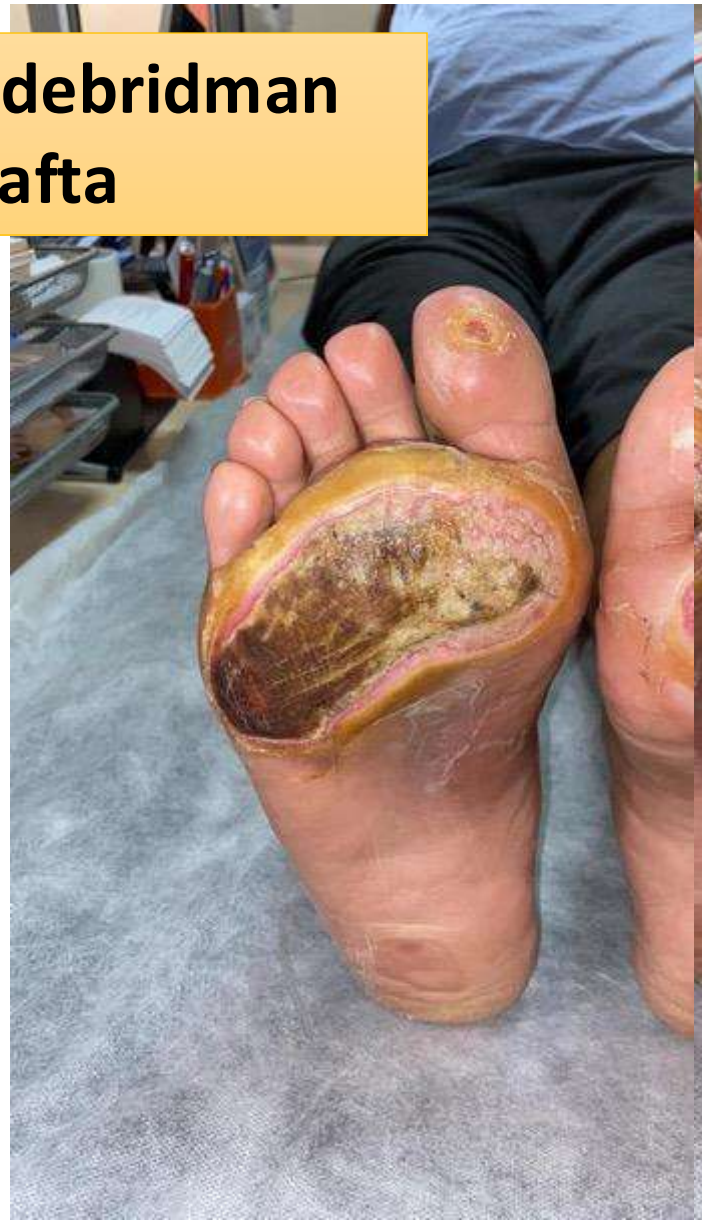
Aslında prensip olarak bir replasman tedavisi uyguluyoruz….

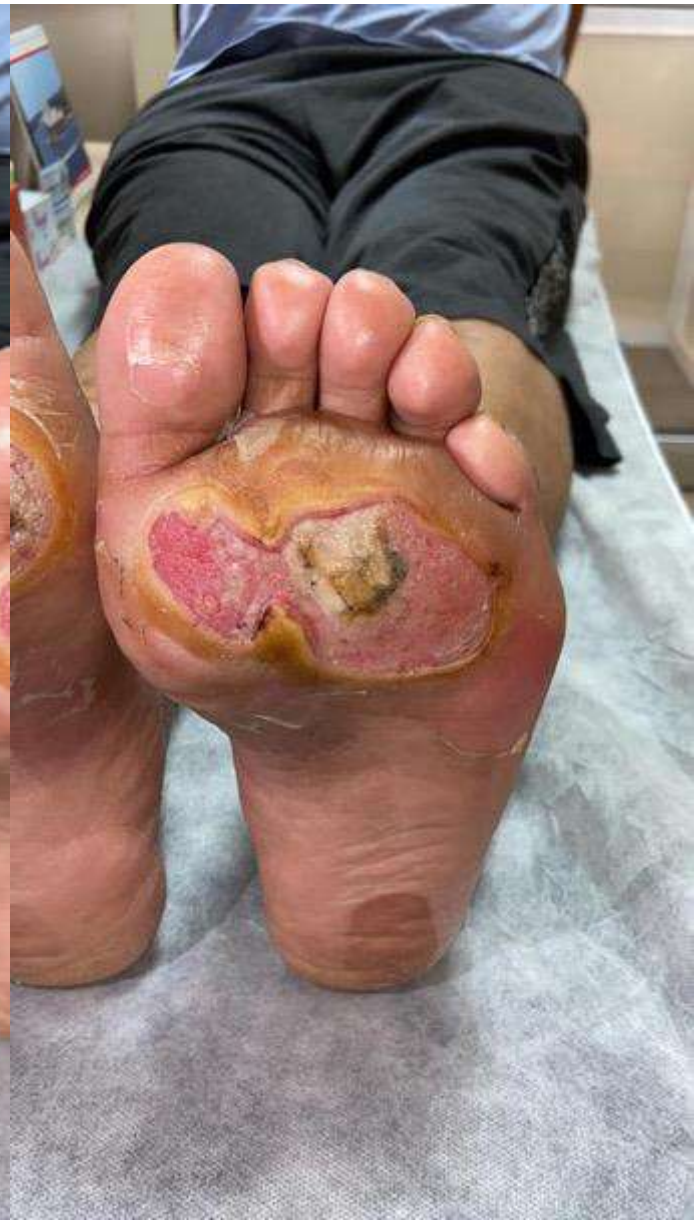
Hasta deneyimleri-1

- 32 yaşında erkek hasta, DM, OAD, 112 kg
- Nöropatisi var…sensoriyel
- Sıcak asfalta basma sonrası ayak tabanında yanık,
- DAİ- grade 2
- Sağ ayak plantar kısmında hassasiyet, YDE?
- Ateş –üşüme –titreme
- Takip ve tedavi amaçlı yatış…
- PE abterapi- SCF

Enzimatik debridman
2 hafta







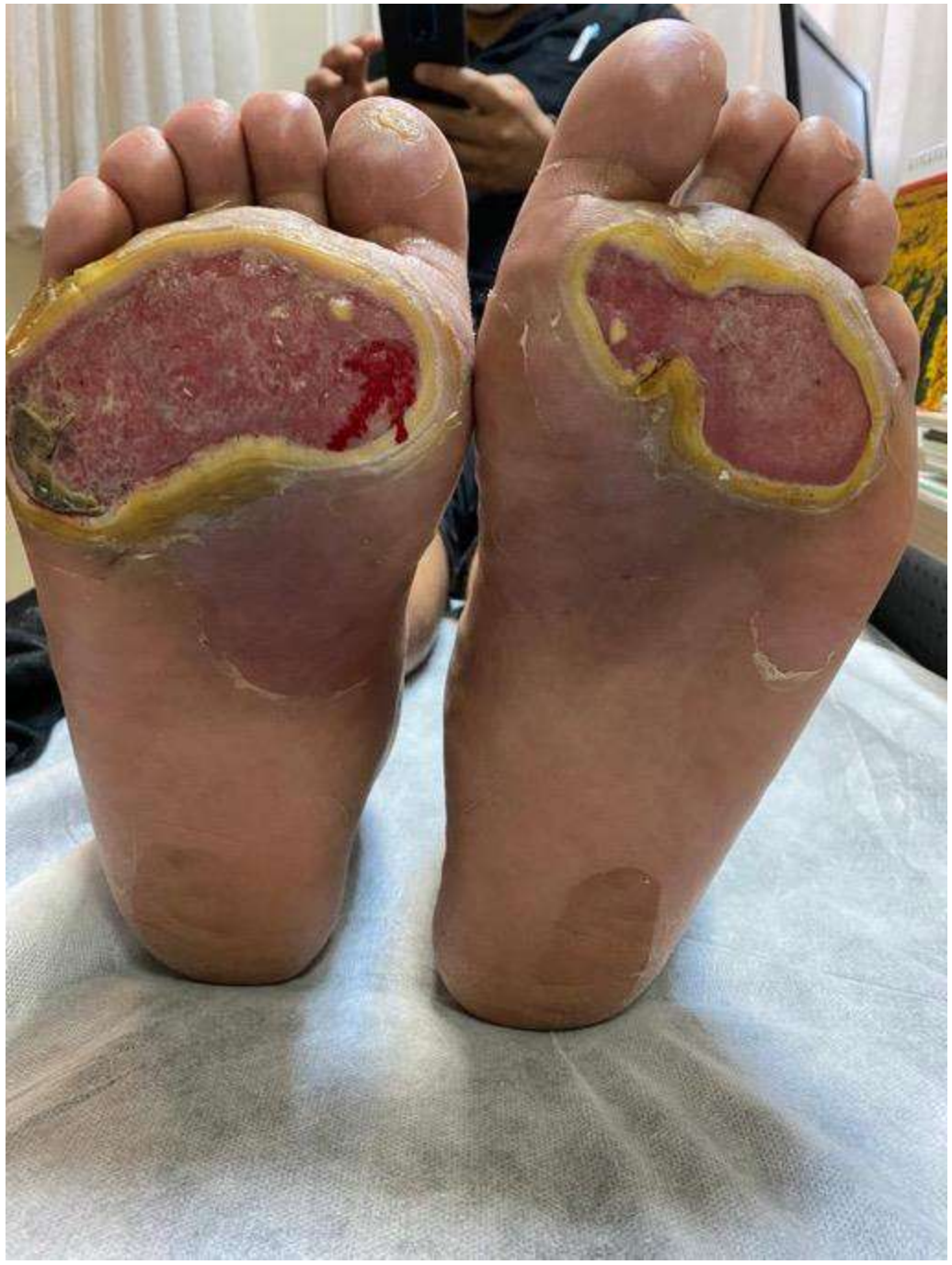
	BK (%PNL)	ESH	CRP	BUN	Kreatinin	eGFR	AST	ALT
1. gün	16,700 (%85)	18	25	18	0.5	98	21	26
3. gün	11.200 (%68)	-	-	21	0.6	91	34	39
5. gün	7.200 (%62)	-	10	17	0.7	90	27	36
7. gün	4.500 (%65)	-	-	21	0.5	99	21	45

Yüzeyel doku USG- abse, koleksiyon yok… minimal cilt altı ödem

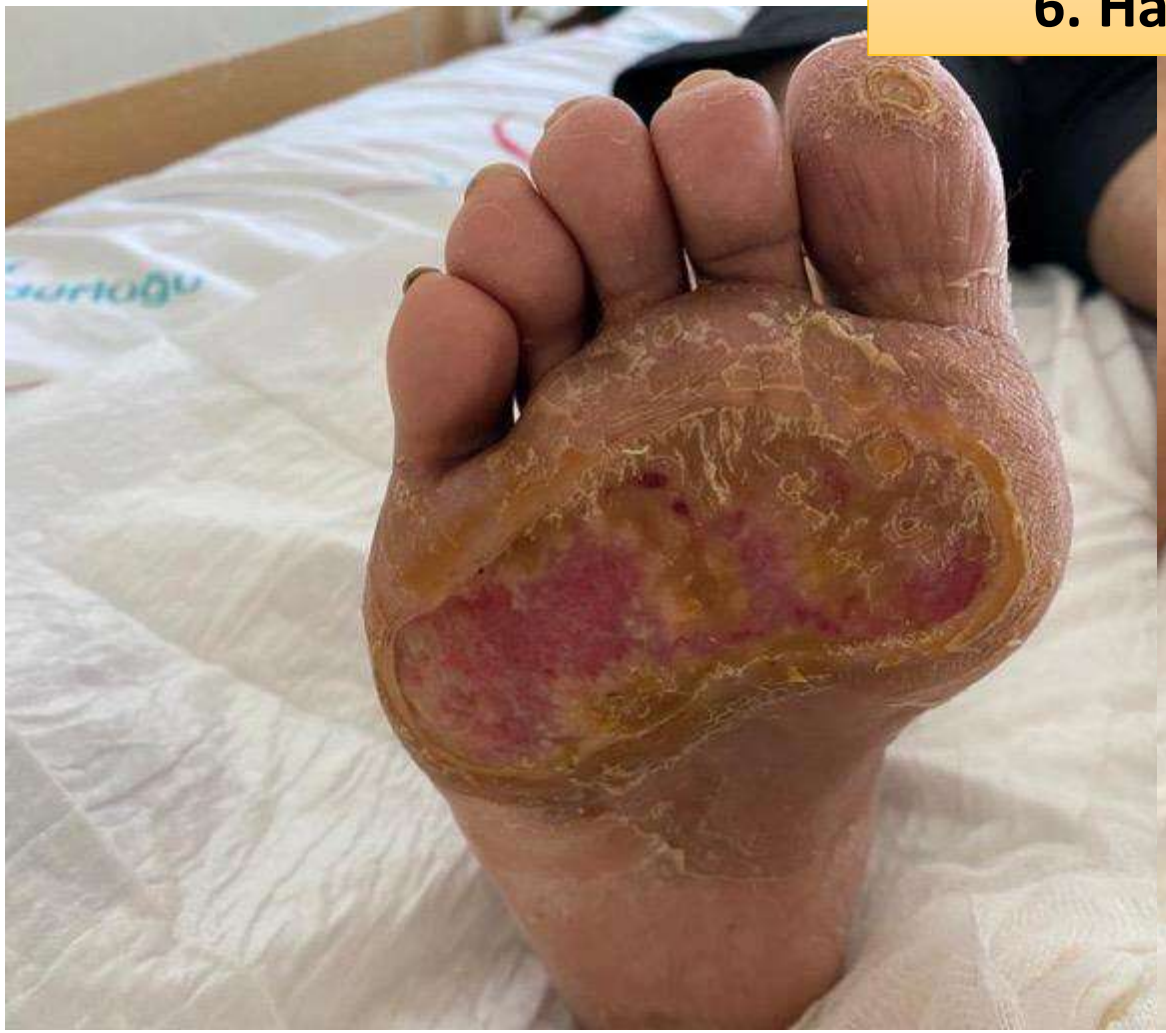
4. Hafta

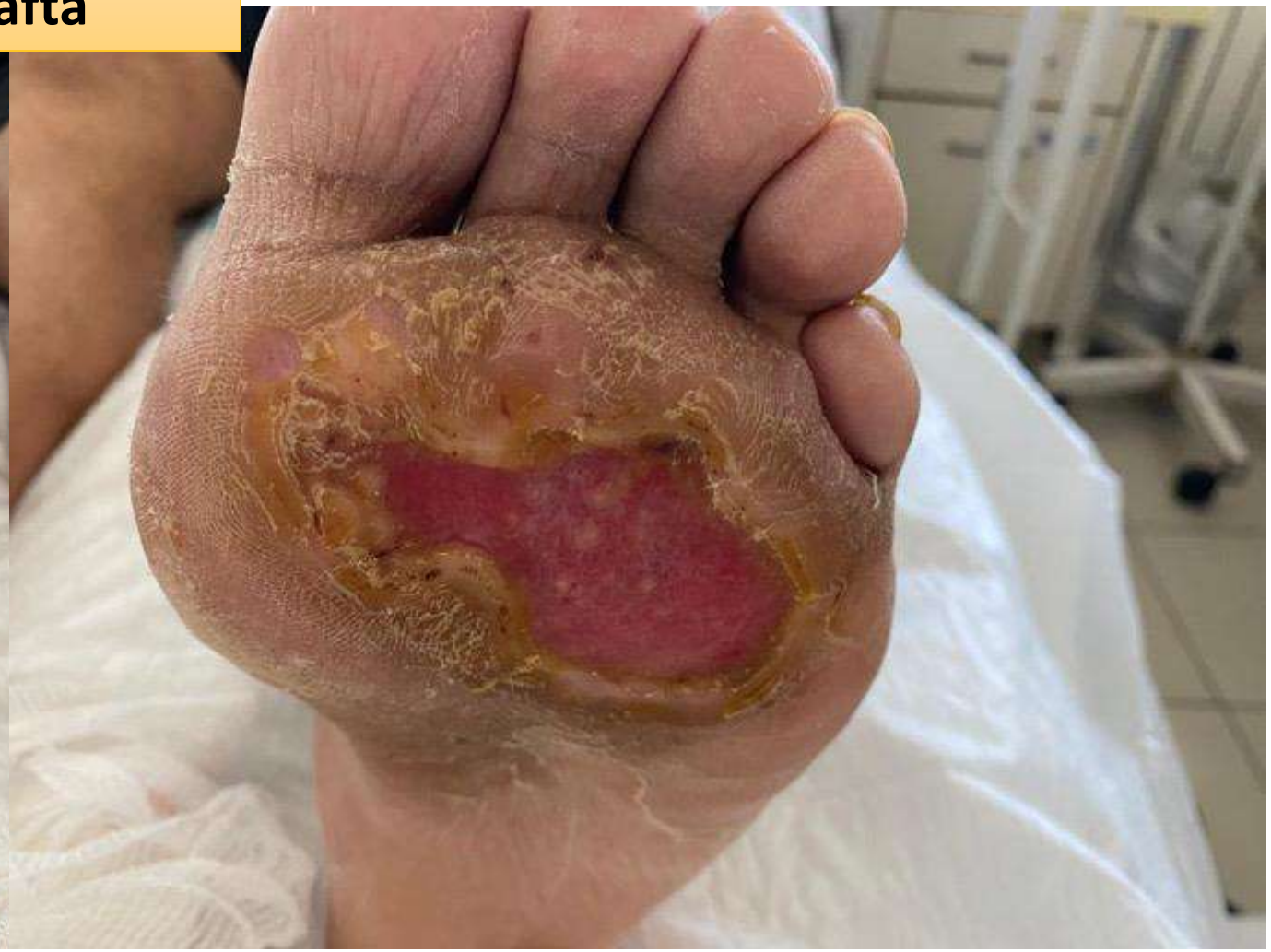
- Granülasyon kısmen var,
- Epitelizasyon nazlı…

- Yara kenarları kaba-keskin debridman
- Yara yatağına Regen D

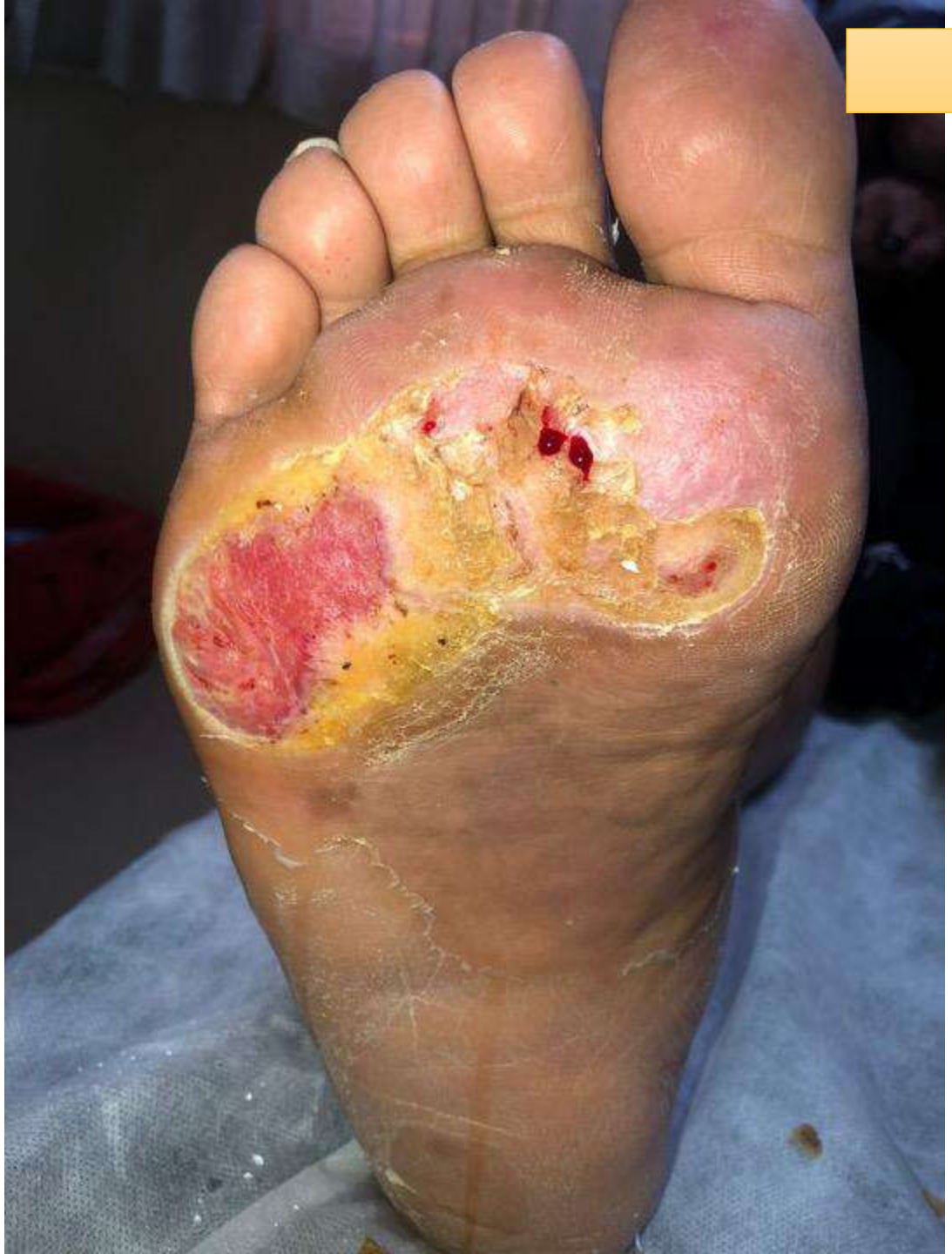


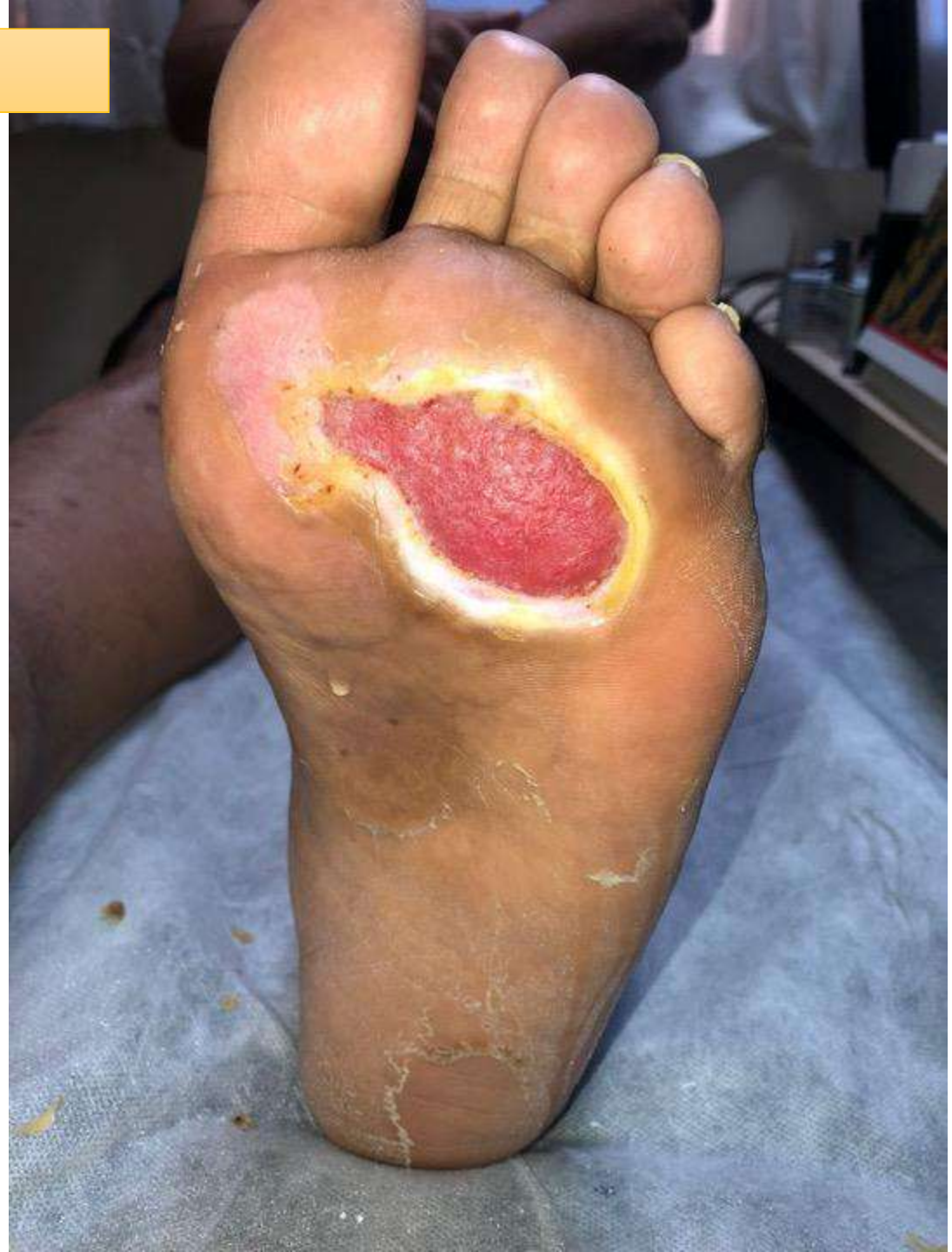
6. Hafta





8. Hafta



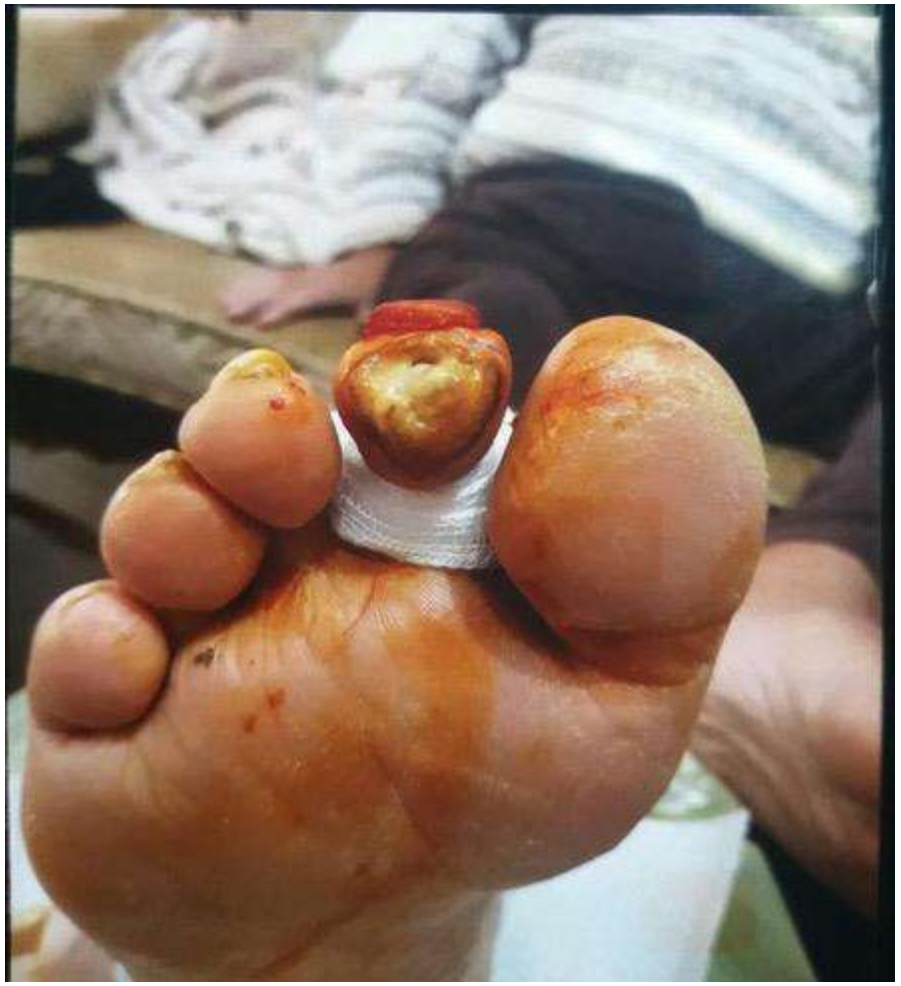


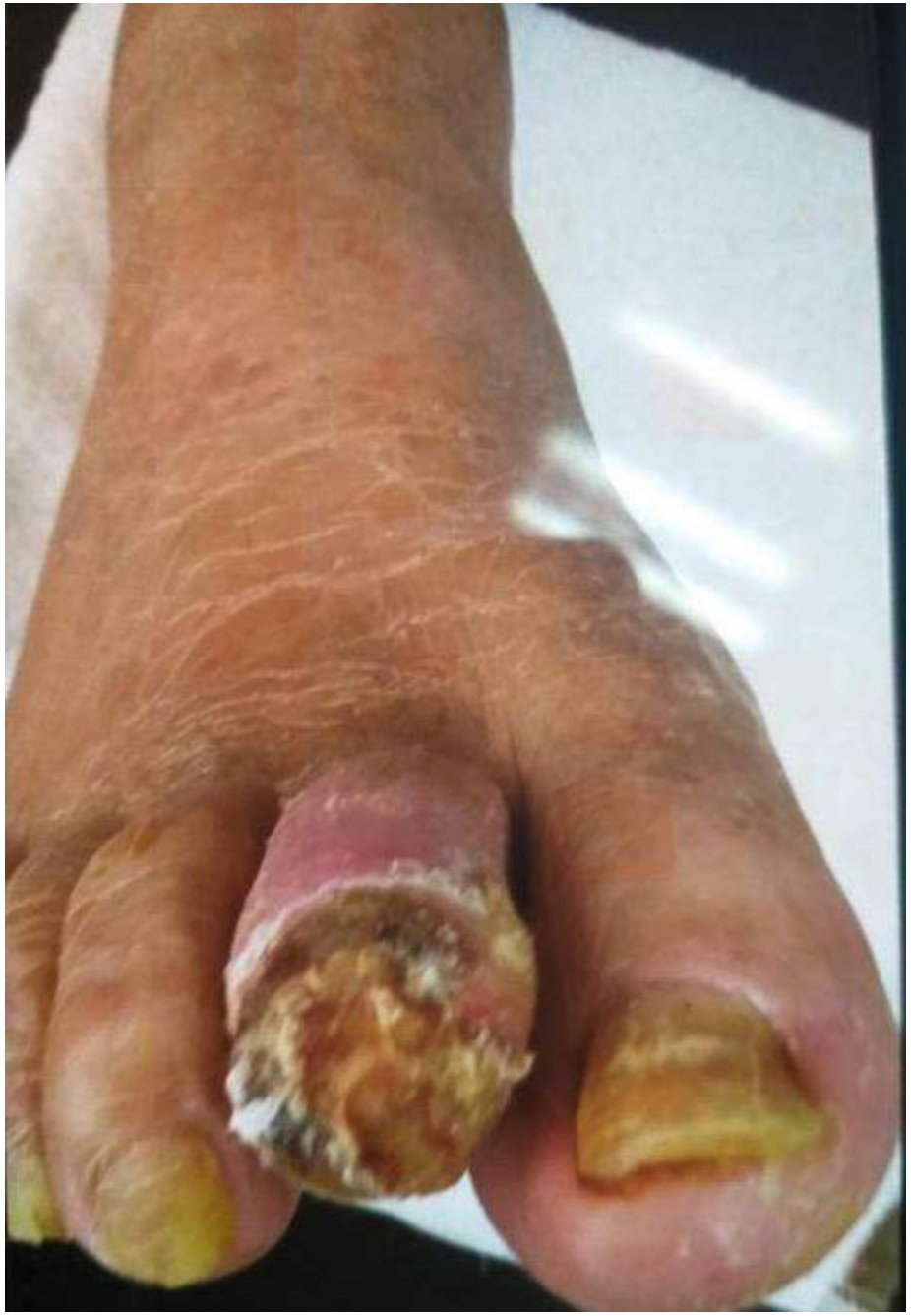
Hasta deneyimleri-2

- 69 yaşında erkek hasta, DM, OAD, 74 kg
- Nöropatisi var, nefropatisi var …
- Ayakkabı vurması sonrası…
- Sağ ayak II. Parmakta DİP'da…DM enfeksiyonu…6. haftada…
- DAİ-grade 3
- PO almış…Enfeksiyon +enflamasyon kontrol altına alınmış,
- ESH, CRP (N)
- Ayak grafisinde 2. parmak distal falanks erimiş…

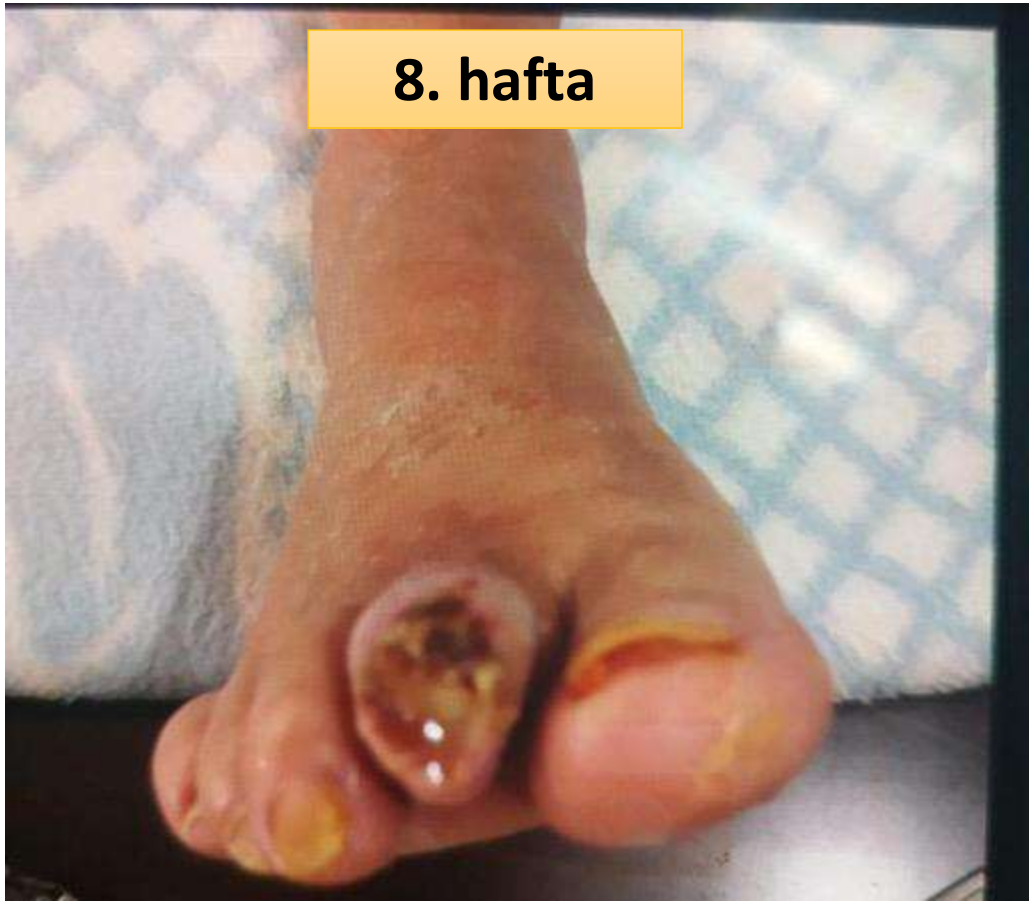
7. hafta

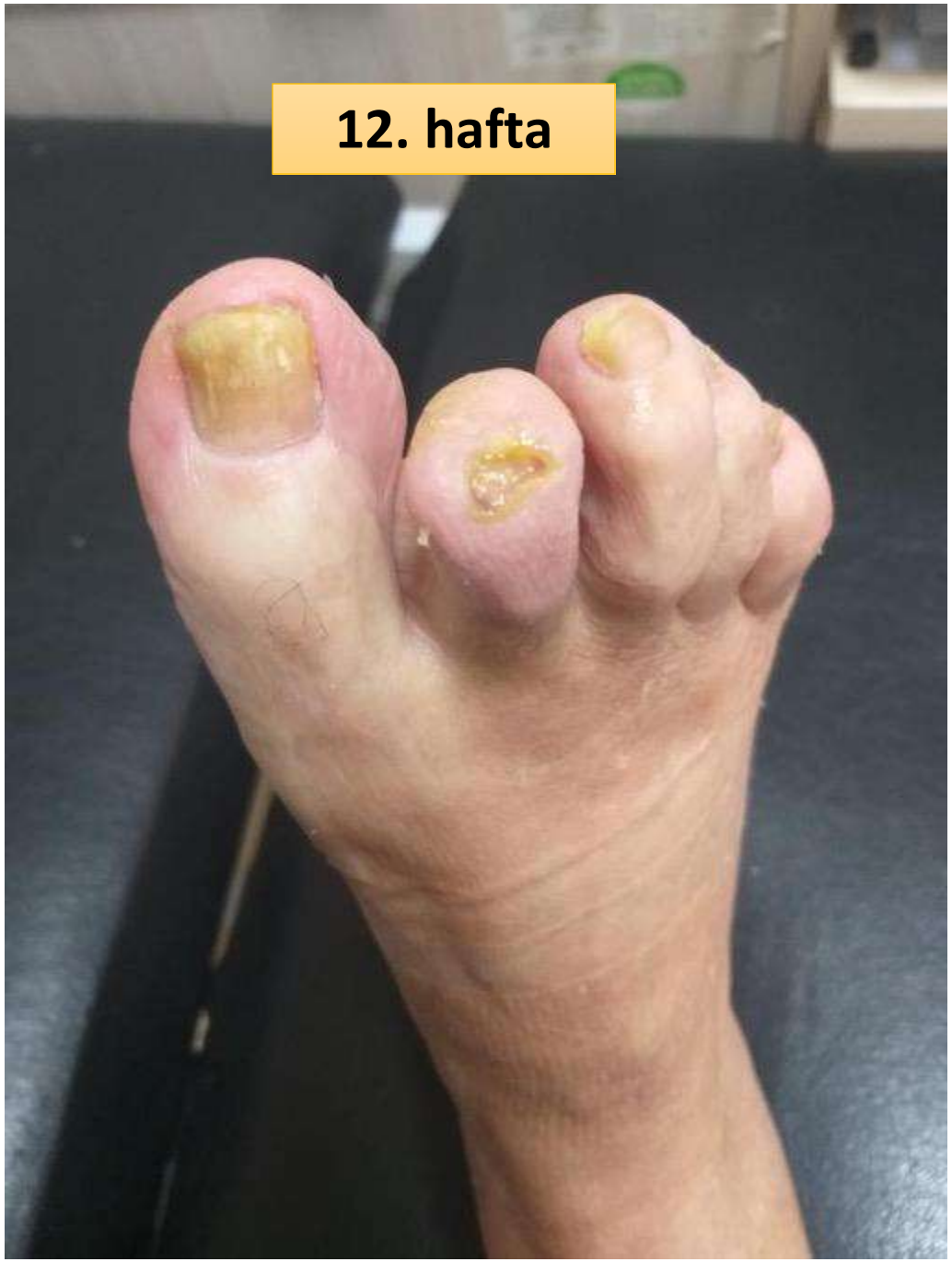
- Lokal pansuman – debridman
- Tırnak + distal falanks kendiliğinden ayrıldı





- Debridman – HOCL
- Regen D-4 hafta

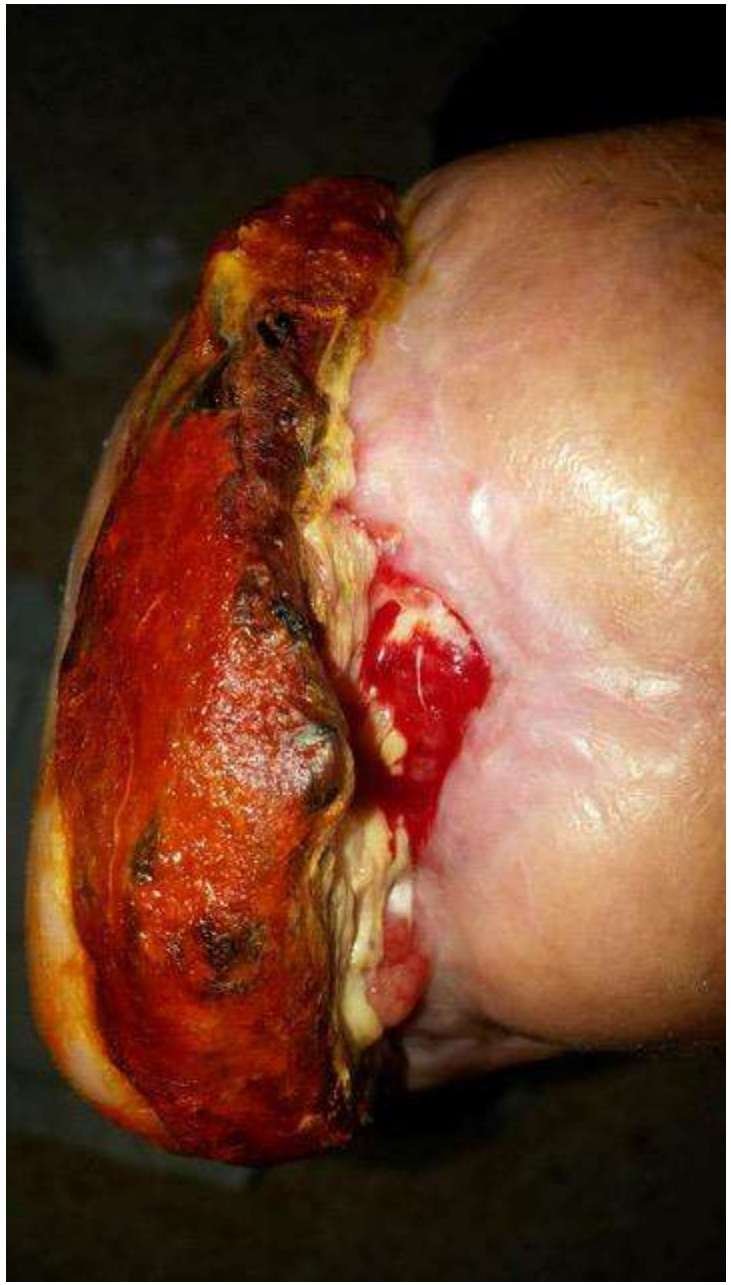




Hasta deneyimleri-3

- 59 yaşında erkek hasta, DM, insülin kullanıyor, 74 kg
- Nöropati-retinopati- nefropati (HD) var …
- Sağ bacak diz altı ampütasyon…DM enfeksiyonu nedeniyle…
- Post op. 6. ayda düşme sonrası güdükte travma…açılma…
- Sonrasında YDE bulgusu- PO antibiyotik… 4 hafta…
- Ödem artmış…
- Güdükte enfeksiyon bulgusu yok,
- ESH, CRP (N)

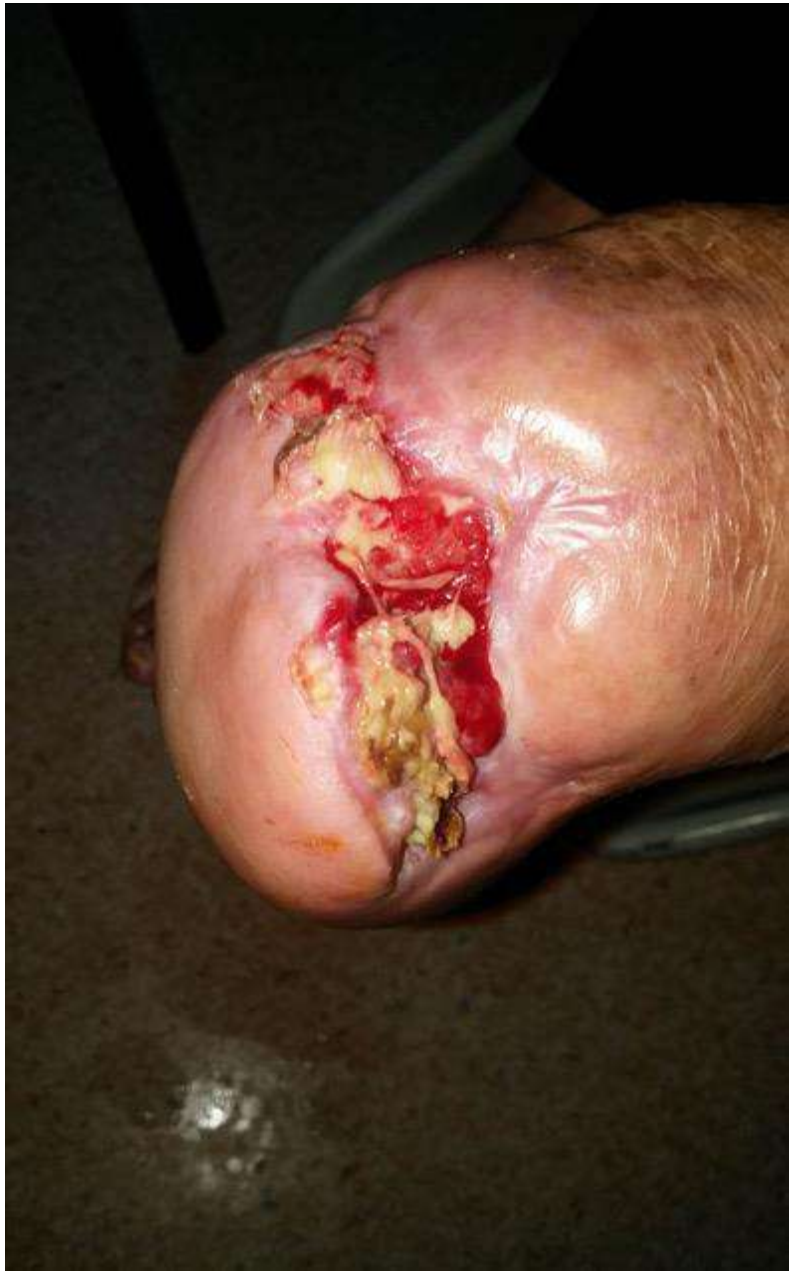
AMPUTASYON SONRASI DİYABETİK HASTADA GÜDÜKTE YARA

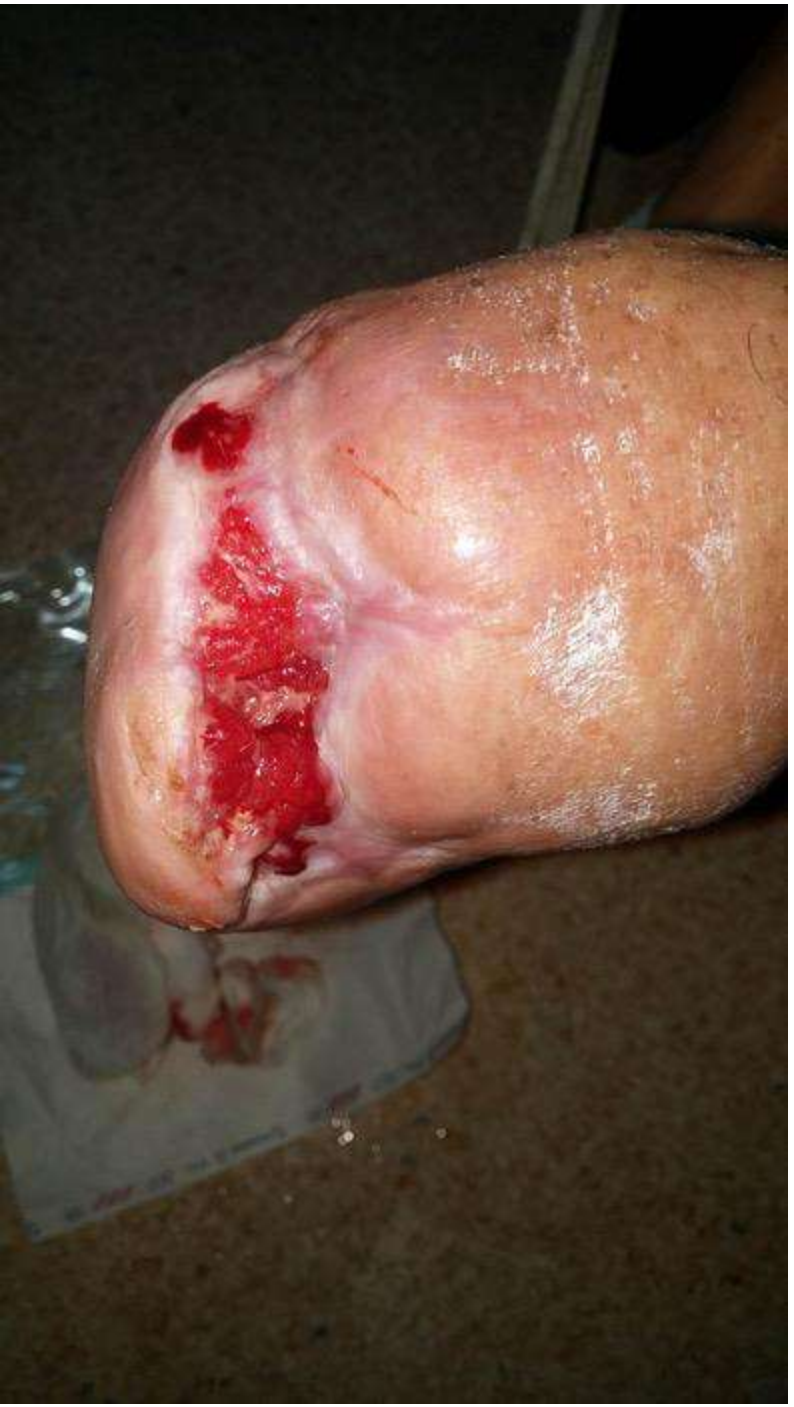


KABUKLU BÖLÜME HİDROJEL,YARA İÇ KISMINA İSE YOĞUN AKINTIDAN DOLAYI GÜMÜŞ İÇERİKLİ FİBER ÖRTÜ VE BARİYER KREM İLE YARA BAKIMINA BAŞLANILDI.

AMK 1 gr tab 2x1

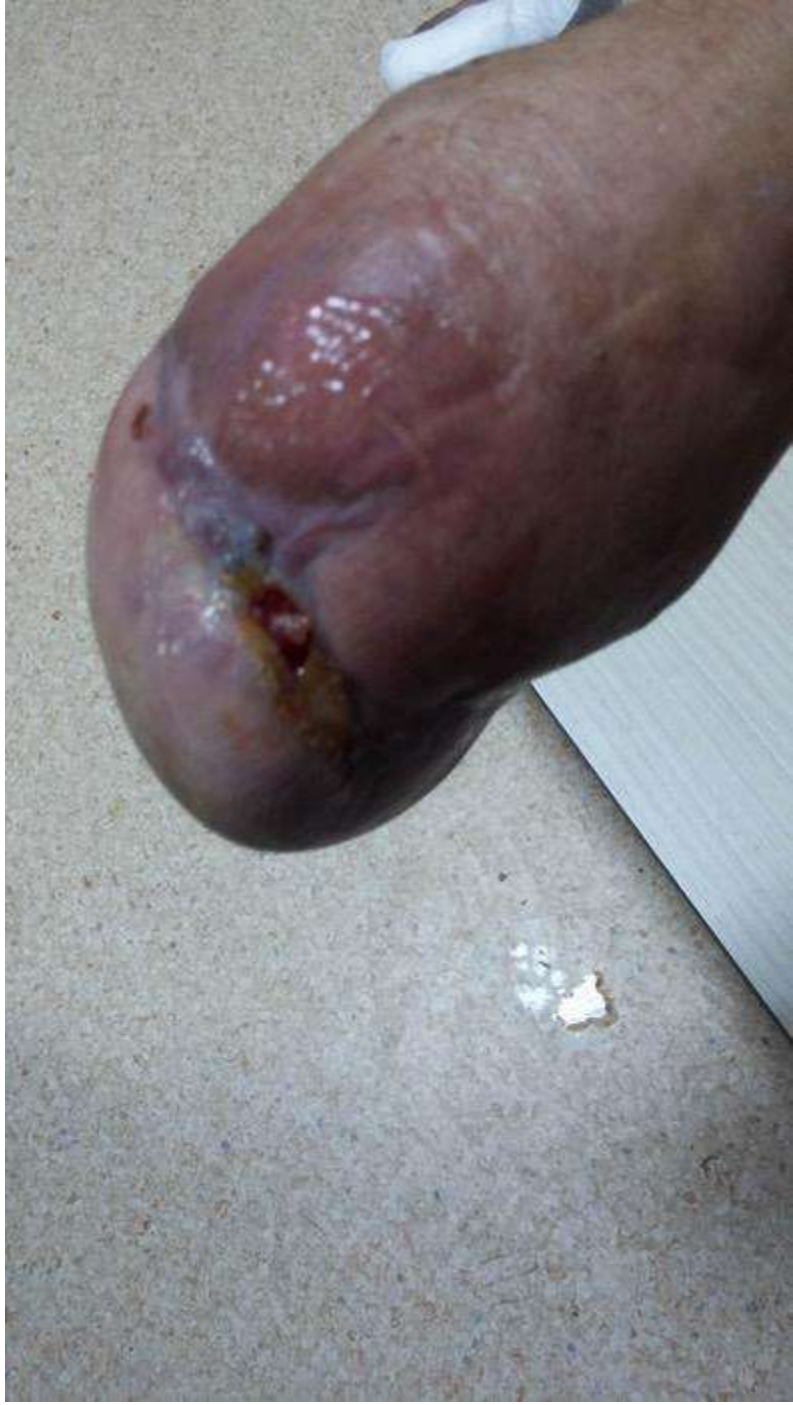
4 hafta sonra …YARADAKİ AKINTI DURDUĞU İÇİN FİBRİNLERİ ÇÖZMEYE YÖNELİK HİDROJEL UYGULAMASINA GEÇİLDİ

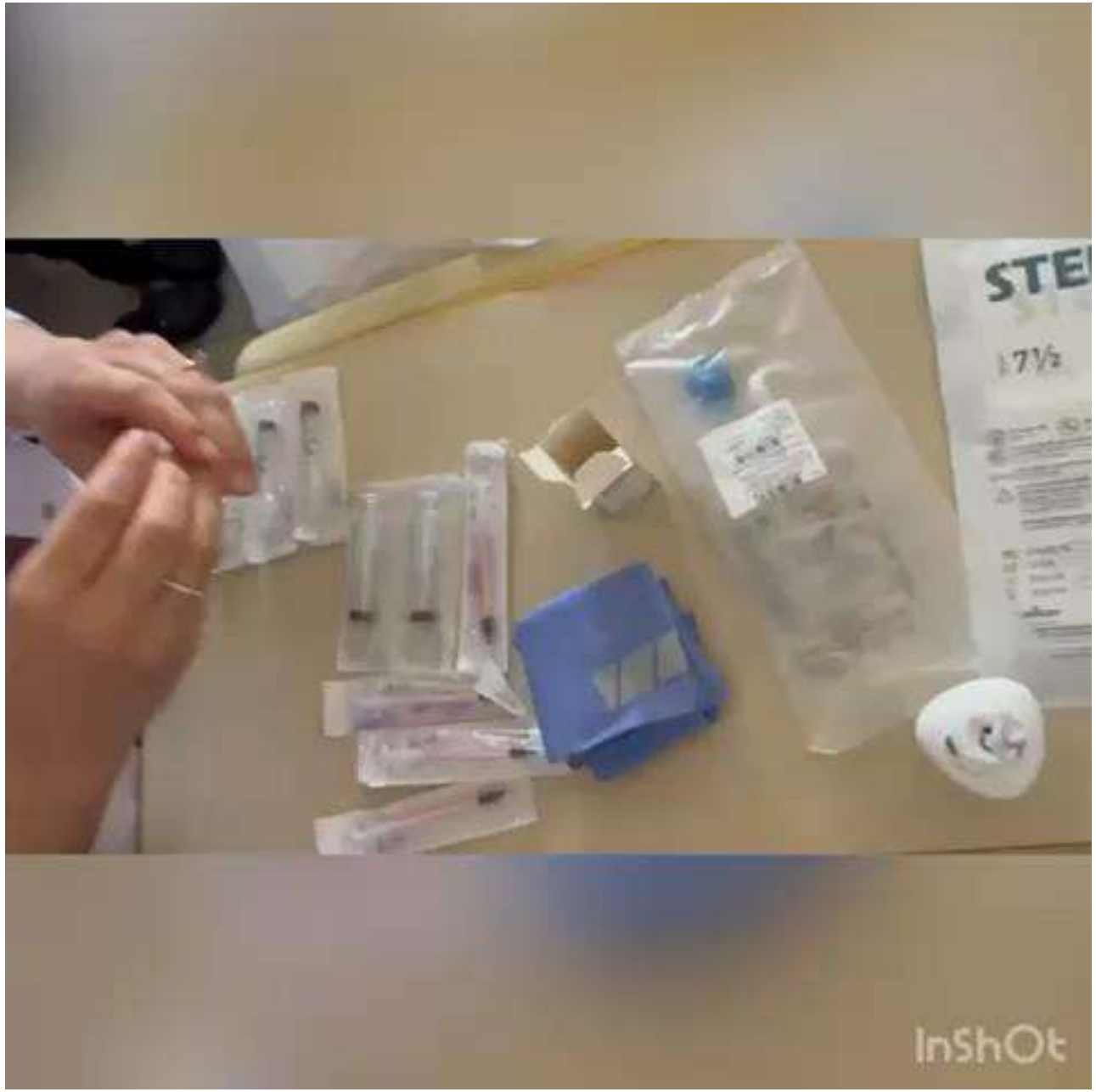




Tedavi 8. haftası…
YARA GRANÜLE VE TEMİZ
OLDUĞUNDAN topikal rhEGF- 4 hf

YARANIN SON DURUMU

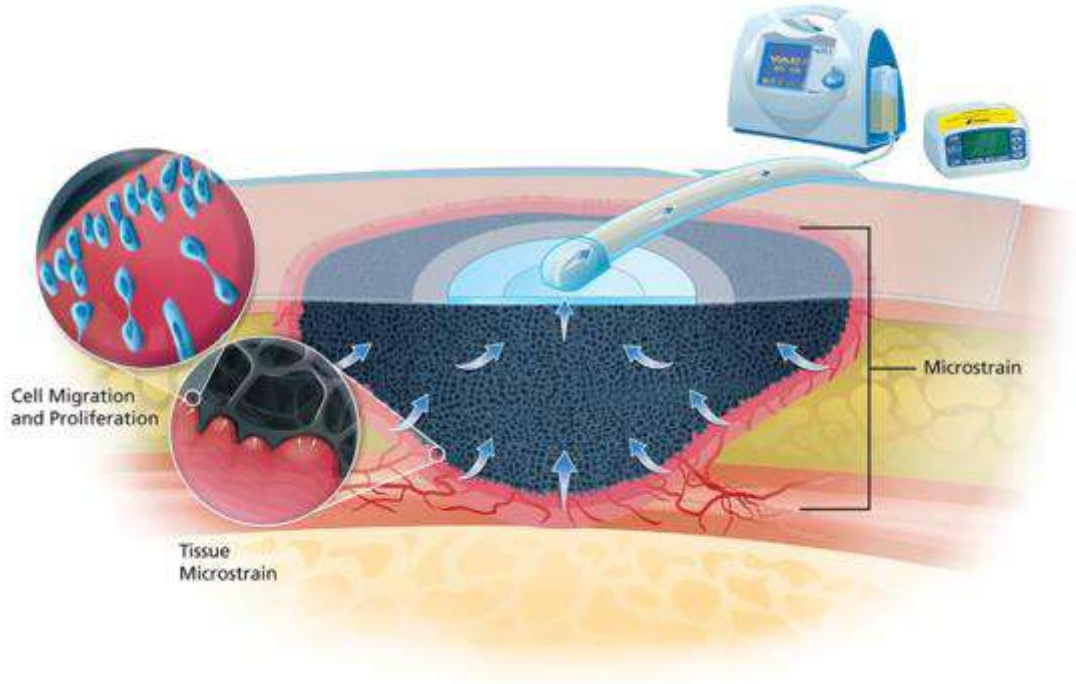



STE
17½
InShOt

VAC=Vacum Asisted Closure
NPWT=Negative Pressure Wound Treatment

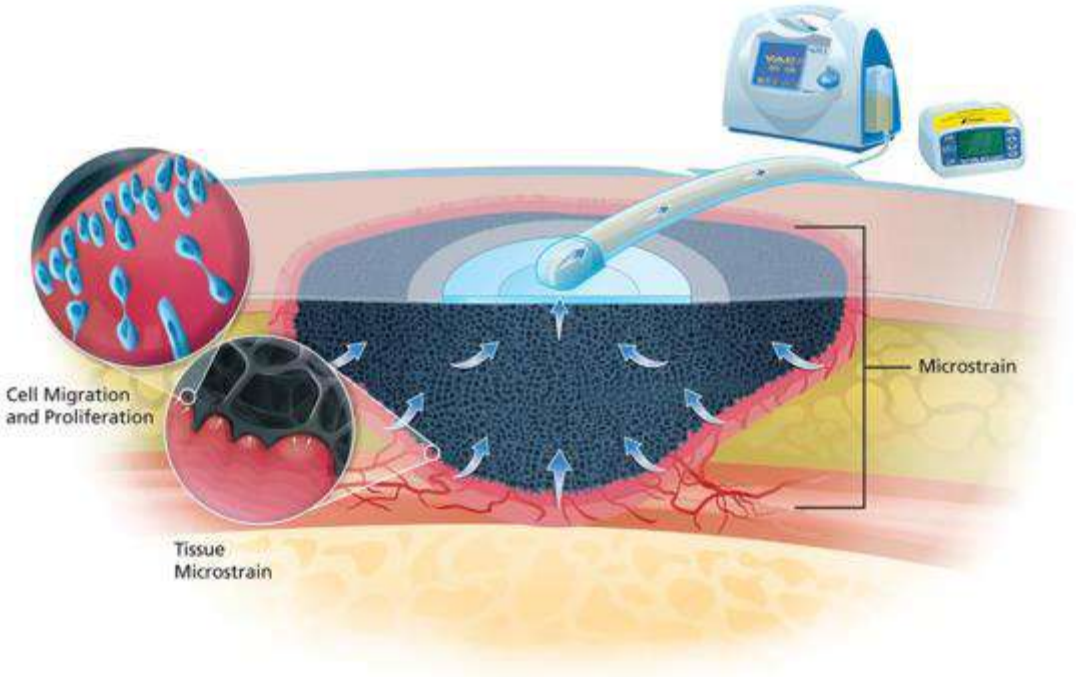
Kontra-Endikasyonları…

- Eskarlı nekrotik doku (?)
- Uygulama alanında kanser,
- Uygulama alanında evisserasyon
- İskemi (?)
- Kontrol altında olmayan koagülopati
- Tedavi-kontrol altında olmayan osteomyelit,
- Enterik veya araştırılmamış fistül



Çalışma prensibi…

- Dokuya sürekli veya belirli aralıklar ile vakum etkisi…
- Vakum ile doku ekspansiyonu ve hücre göçü ve proliferasyon…
- Yıkamalı ise; debris ve biyofilmin emilmesi…
- Sünger gümüş ise; antimikrobiyal etki…



Uygulama...DIM

- D:debridman
- I:İnfeksiyon ve inflamasyon kontroli
- M:Nem dengesi
- -20 ila -200 mmHg doku basıncı?
- Sürekli veya aralıklı ?
- Yıkamalı-sız ?
- 2 veya 3 günde bir değişim ?

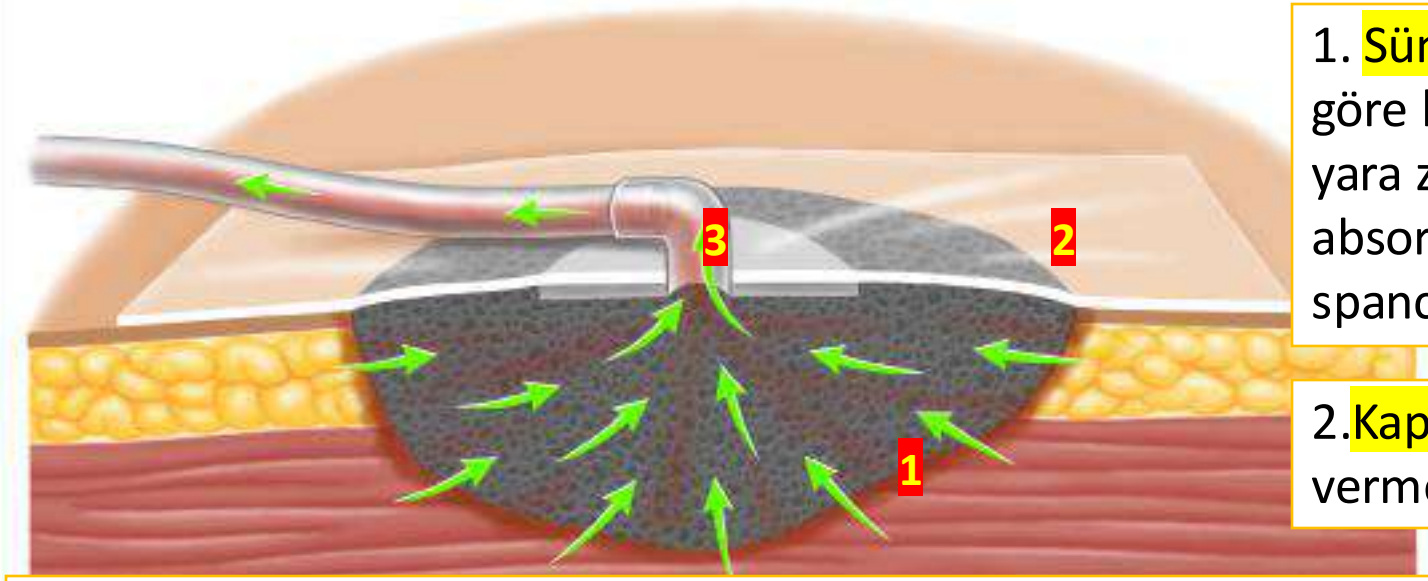
Düşük ve yüksek basınç kavramları

- < -75 mmHg düşük
- > -125 mmHg yüksek

- Aralıklı basınç uygulaması daha çok yıkama yapılacak ise
- Devamlı veya aralıklı veya kombinasyonlar …

- En kısa 2 gün- en uzun 5 gün
- Uygulama sıklığına pansumanın durumuna göre karar verilir…süngerde deformasyon, pansumanda kaçak, sızdırma, maserasyon vb…

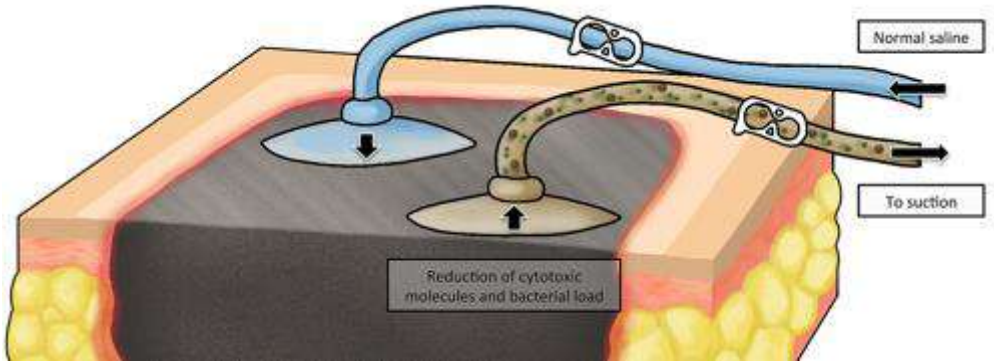
VAC=Vacuum Asisted Closure
NPWT= Negative Pressure Wound Treatment



1. Sünger- Poliürethan, adhesive olmayan, dokuya göre kesilmiş, doku kenarlarını taşmadan yerleştirilir yara zemininde tendon, damar, sinir paketi var ise absorpsiyondan minumum etkilenmesi için üstüne spanch, vicriyl, beyaz sünger kademe yapılabilir

2.Kapama-şefaf, cildi tahriş etmeyecek, sıvı akışına izin vermeyecek adhesive olmalıdır..

3.Vakum- negatif atmosferik basınçta; -50 ila -175…dokuya göre vakum basıncı seçilebilir, ağrı/kanama var ise basınç düşürülür… basınç aralıklı veya sürekli olabilir… yıkamalı olabili…yıkamalı da SF/antiseptik ile yara yatağıda sıvı verilir ve belli süre bekledikten sonra geri emilir…etkin vakumda sünger ebatı en az %80 azalır…



4. Toplama kabı-canister…

Ubbink DT, Westerbos SJ, Nelson EA, Vermeulen H. A systematic review of topical negative pressure therapy for acute and chronic wounds. Br J Surg 2008; 95:685.

Makro düzeyde olanlar?

Mikro düzeyde olanlar?

Negatif basınç altında köpük ile yara yüzeyi teması…
1.mikrodeformasyon,
2.hücre uzaması

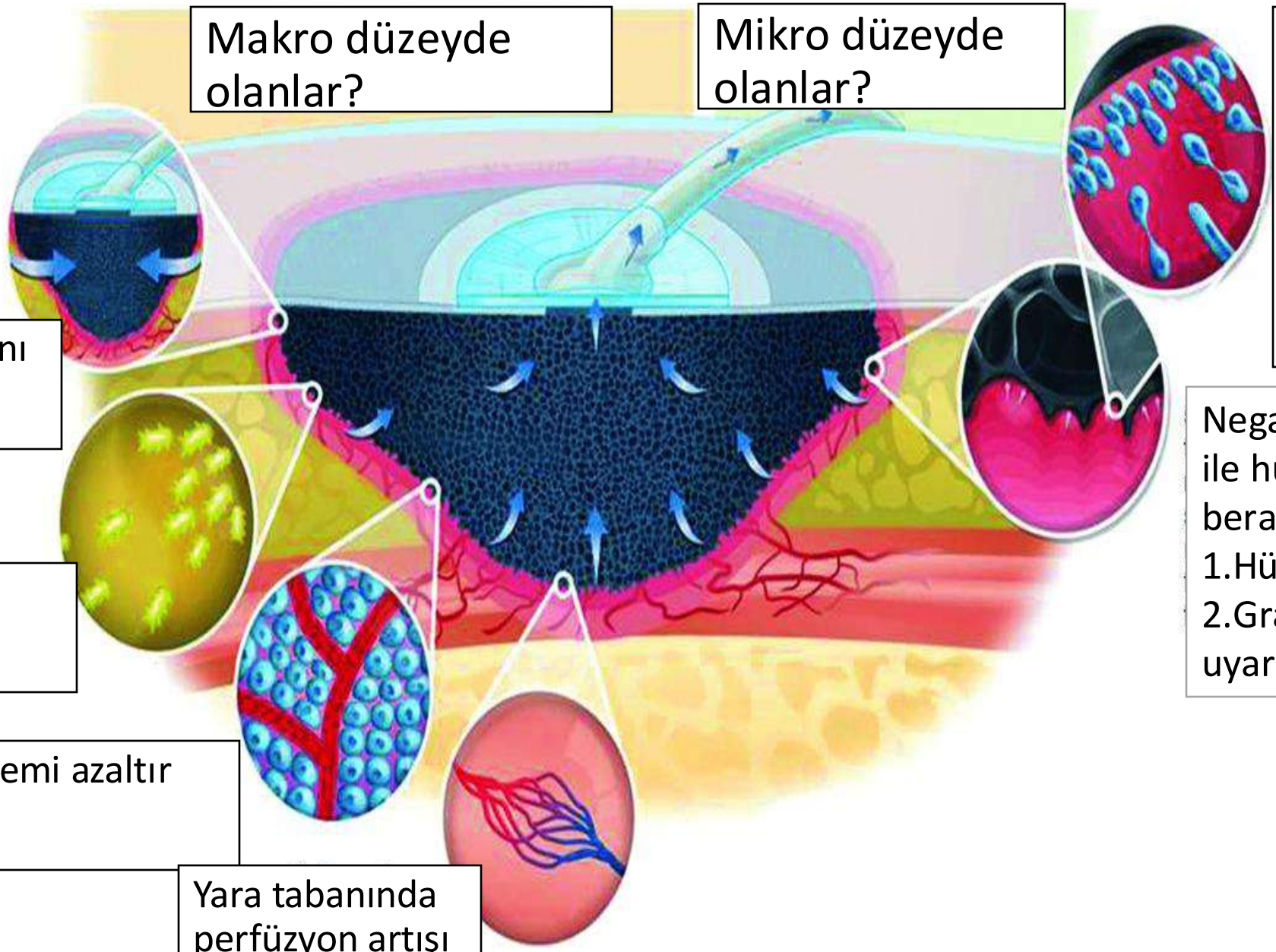
Yara kenarlarını yaklaştırır

Enfeksiyonu uzaklaştırır

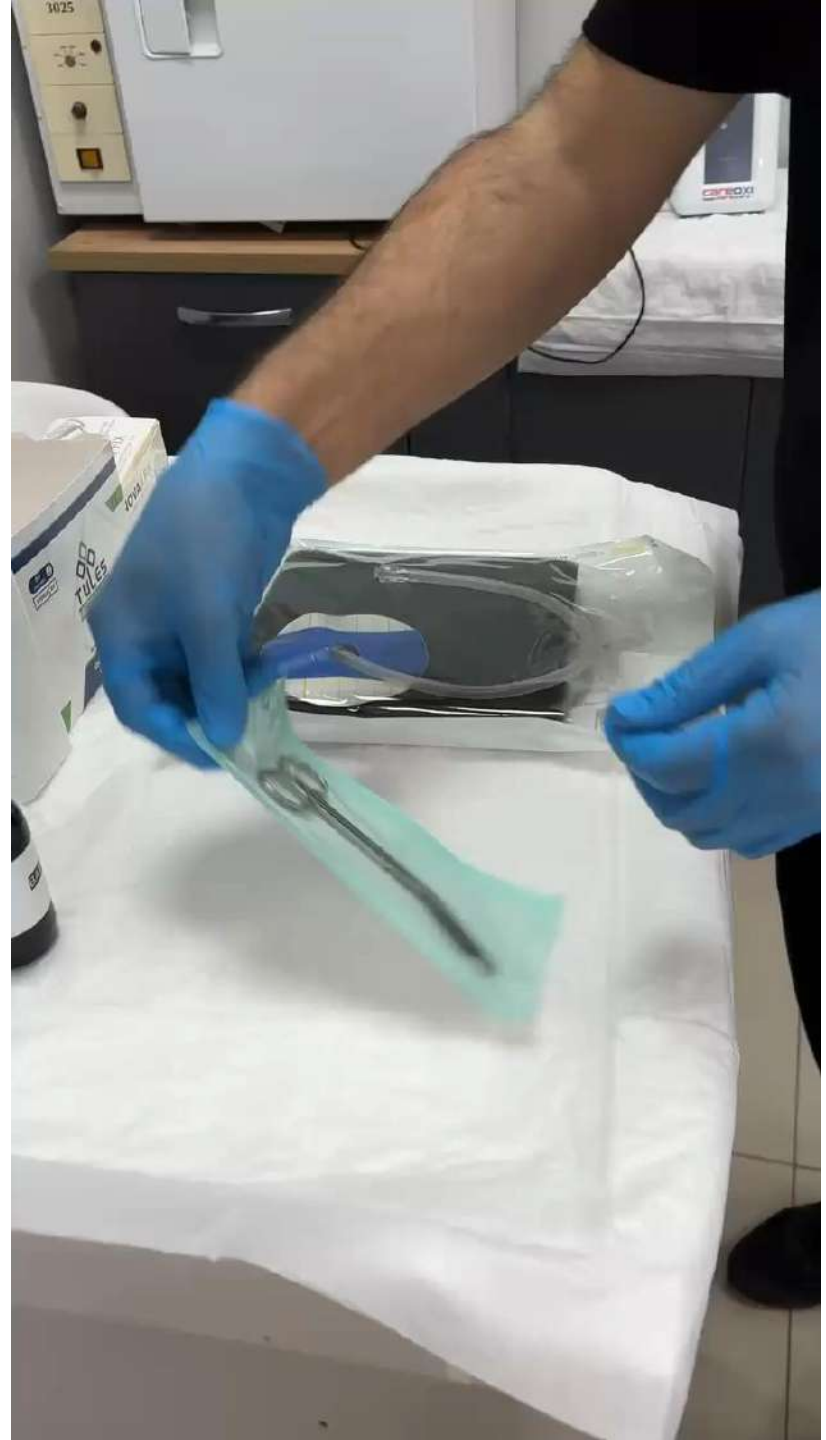
Ödemi azaltır

Yara tabanında perfüzyon artışı

Negatif basınç etkisi ile hücre uzaması beraberinde
1.Hücre bölünmesi
2.Granülasyon uyarılır



J Deutsche Derma Gesell, Volume: 14, Issue: 8, Pages: 786-795, First published: 10 August 2016, DOI: (10.1111/ddg.13038)


3025
rules

Etkinlik değerlendirmesi?

- Fikir birliği yok…
- Akut yarada tamamen kapanma?
- Kronik yarada…
  - -En x boy x derinlikten herhangi birinde %50'den fazla değişim
  - -Yüzey alanında küçülme…cm^2
  - -İnfeksiyon veya inflamasyonda (ödem) gerileme
  - -Cerrahi için uygun ebata düşme

Zens et al. Systematic Reviews (2020) 9:238
https://doi.org/10.1186/s13643-020-01476-6

Systematic Reviews

RESEARCH Open Access

Negative pressure wound therapy in patients with wounds healing by secondary intention: a systematic review and meta-analysis of randomised controlled trials

Yvonne Zens[1*], Michael Barth, Heiner C. Bucher[2], Katrin Dreck[1], Moritz Felsch[1], Wolfram Groß[1], Thomas Jaschinski[1], Heike Kölsch[1], Mandy Kromp[1], Inga Overesch[1], Stefan Sauerland[1] and Sven Gregor[3]

- Randomize kontrollü çalışmaların metaanalizi
- İlk taramada uyumlu…317 çalışma…
- Kriterleri karşılayan …48 çalışma değerlendirilmiş
- 1386 hasta…

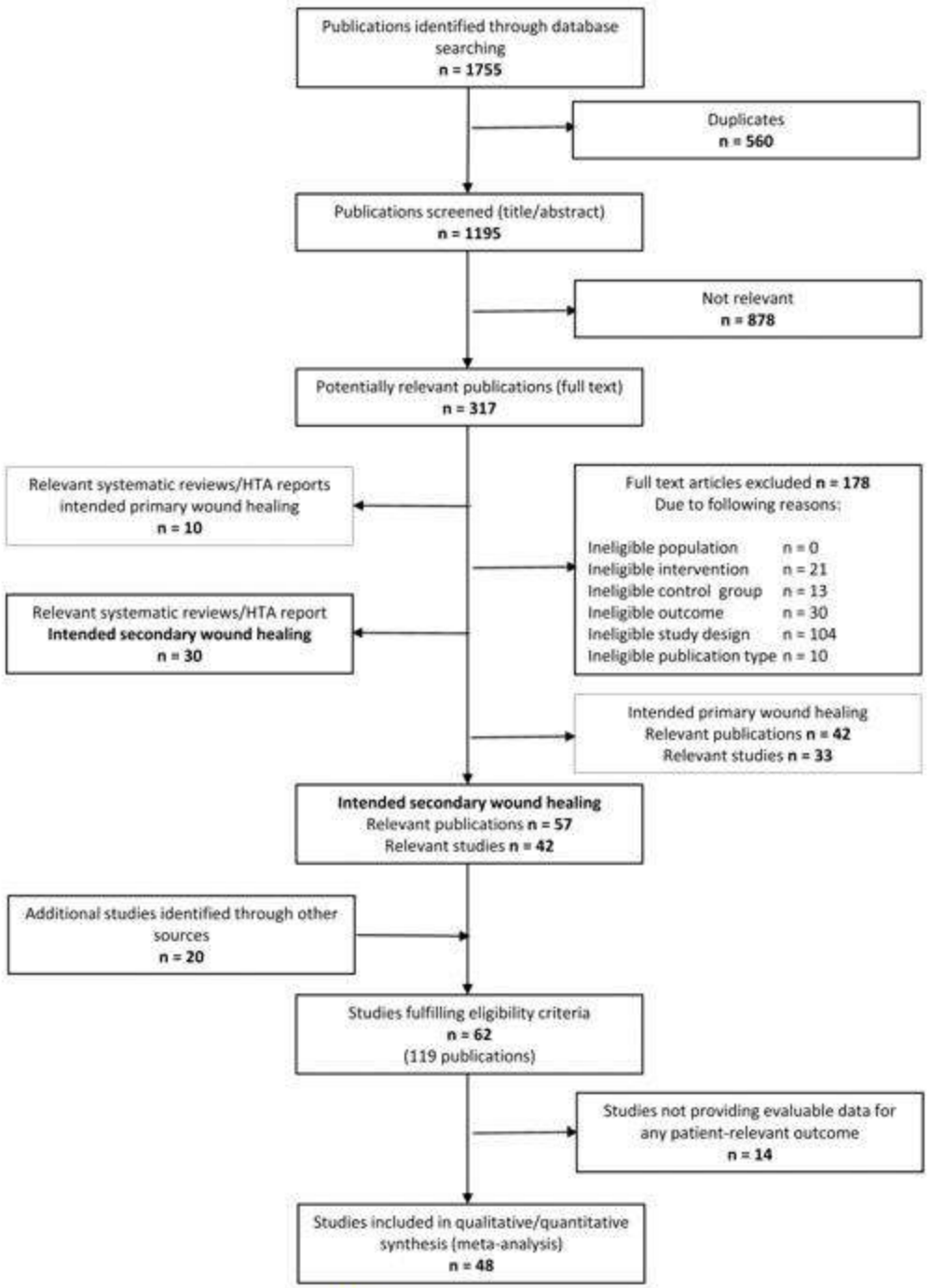


Fig. 1 Flowchart of study selection (based on Moher et al. [11])

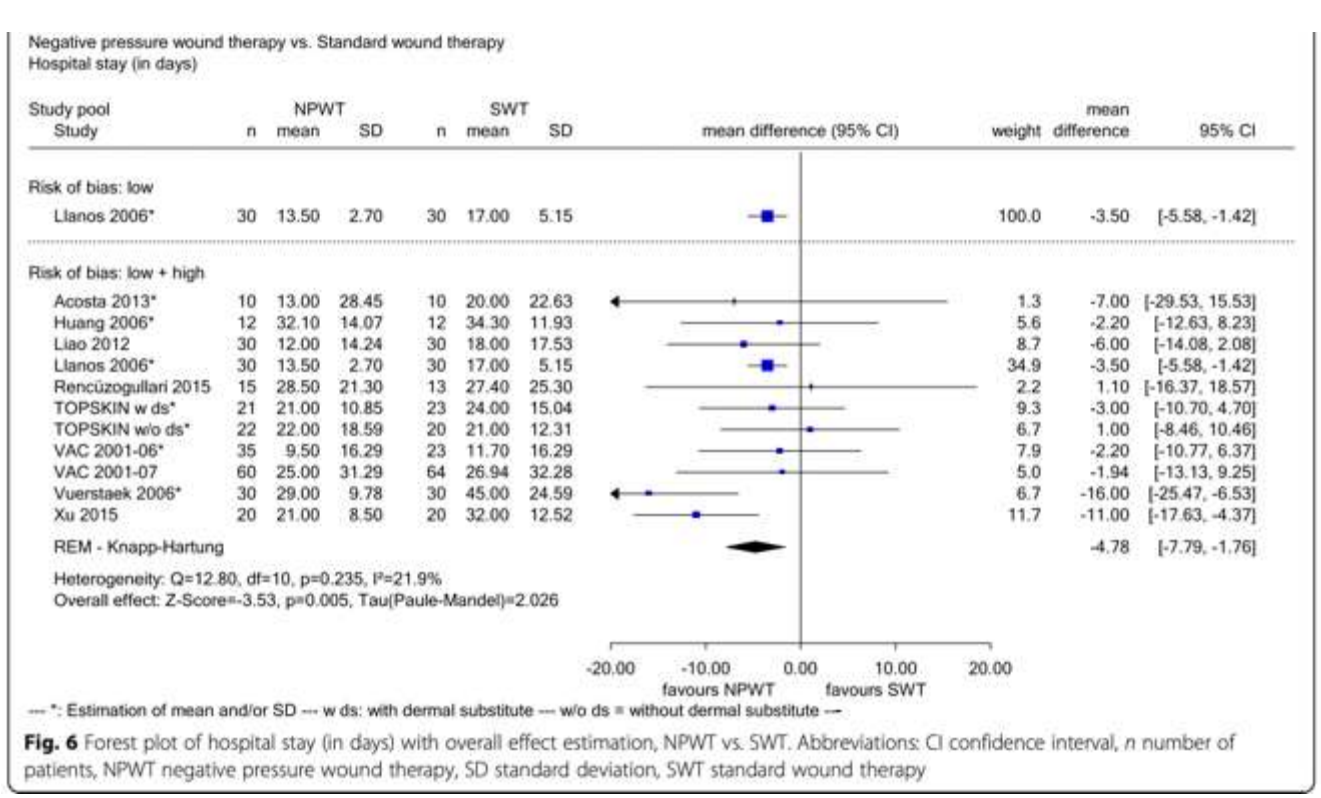


Fig. 6 Forest plot of hospital stay (in days) with overall effect estimation, NPWT vs. SWT. Abbreviations: CI confidence interval, *n* number of patients, NPWT negative pressure wound therapy, SD standard deviation, SWT standard wound therapy

NPWT

Hastanede yatış süresi ortalama 1 hf kısa

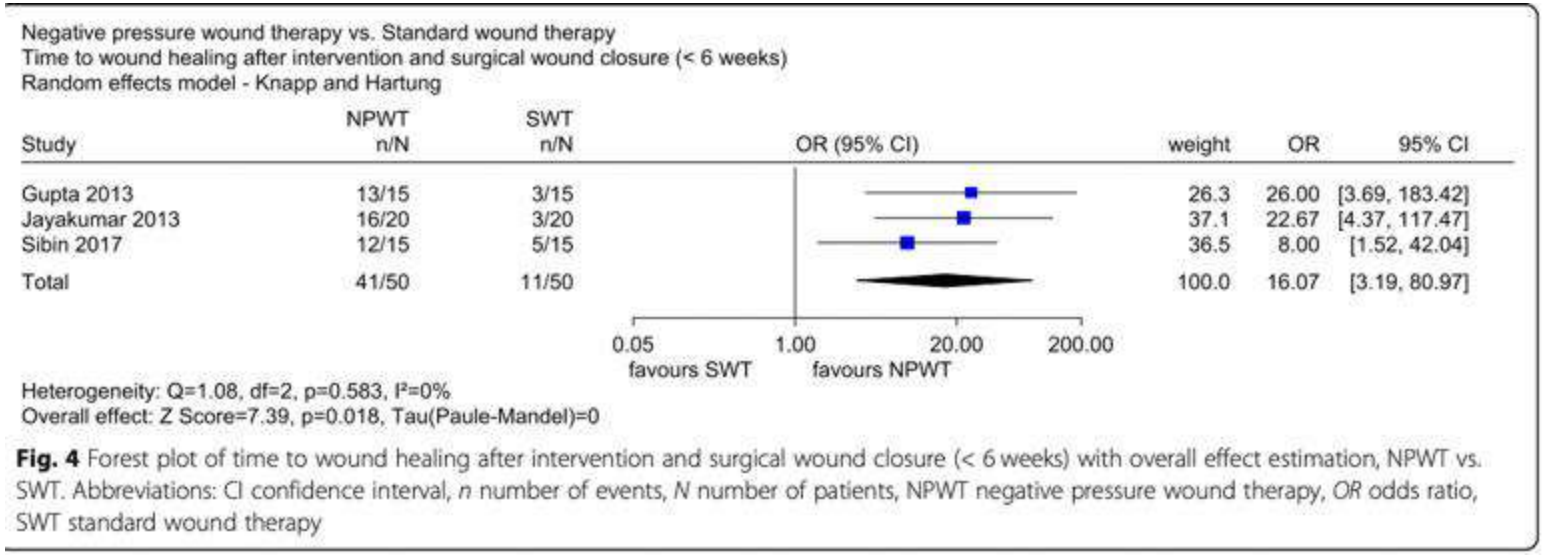


Fig. 4 Forest plot of time to wound healing after intervention and surgical wound closure (< 6 weeks) with overall effect estimation, NPWT vs. SWT. Abbreviations: CI confidence interval, *n* number of events, *N* number of patients, NPWT negative pressure wound therapy, *OR* odds ratio, SWT standard wound therapy

NPWT

Cerrahiye giden kapanma < 6hf

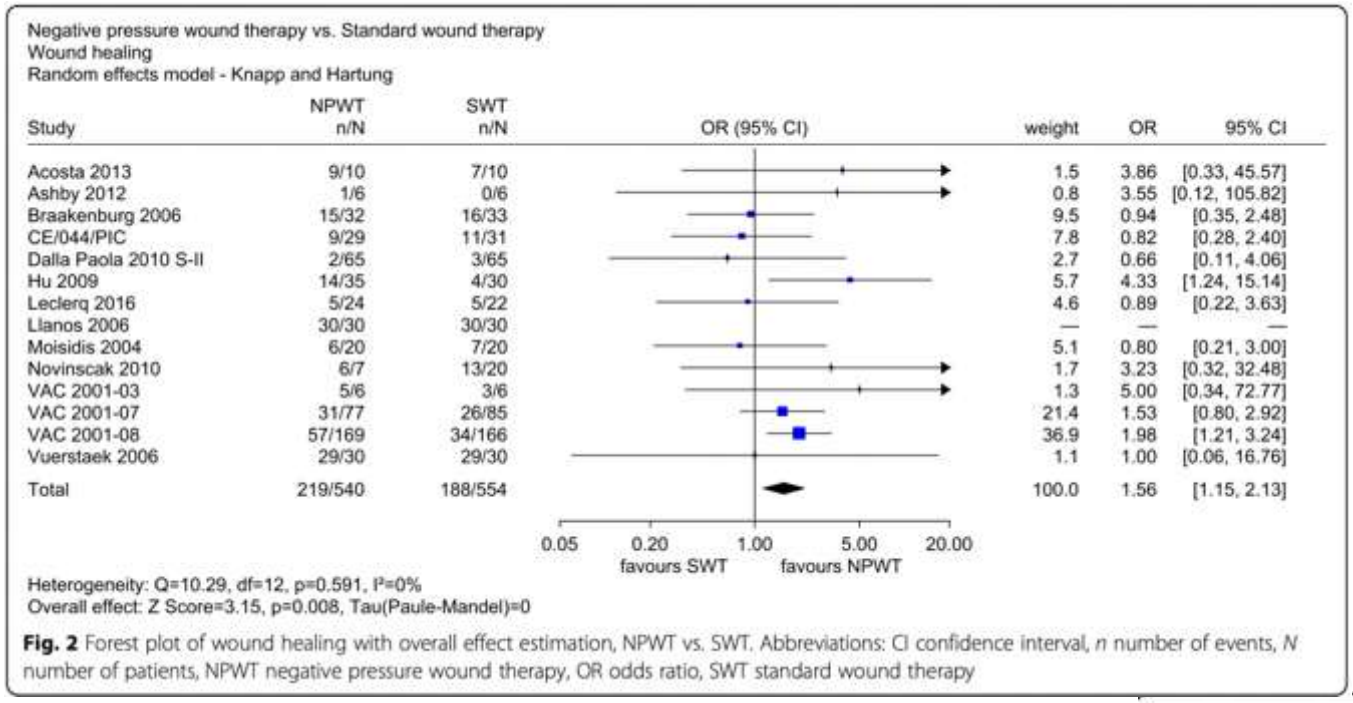


Fig. 2 Forest plot of wound healing with overall effect estimation, NPWT vs. SWT. Abbreviations: CI confidence interval, *n* number of events, *N* number of patients, NPWT negative pressure wound therapy, OR odds ratio, SWT standard wound therapy

NPWT

İle yara iyileşmesi daha fazla 3.15 kat

NPWT

İle yara iyileşmesi daha hızlı 4.72 kat

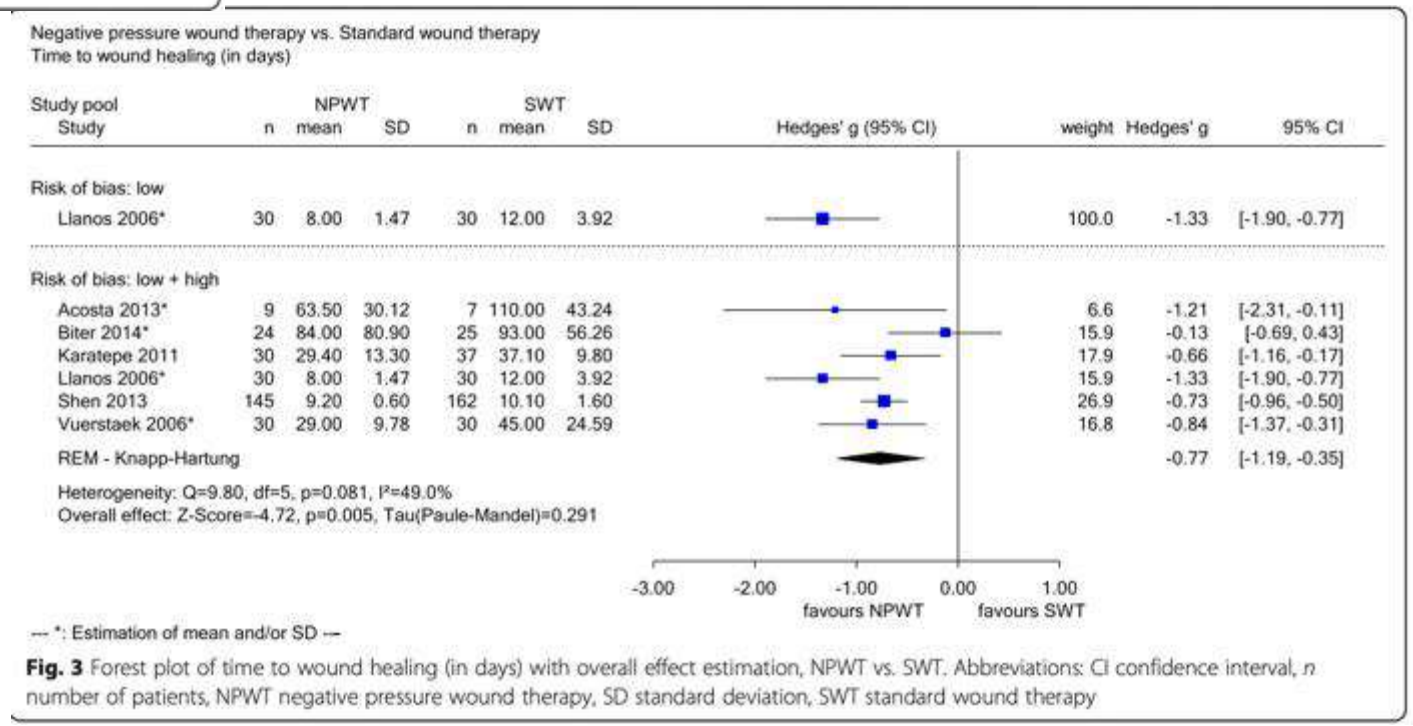


Fig. 3 Forest plot of time to wound healing (in days) with overall effect estimation, NPWT vs. SWT. Abbreviations: CI confidence interval, *n* number of patients, NPWT negative pressure wound therapy, SD standard deviation, SWT standard wound therapy

Profilaktik kullanımı…

- Abdominal ve pelvik cerrahide
- Vasküler cerrahide
- Ortopedik cerrahide

PROMISES RCT çalışması
Profilaktik NPWT diz artroplastisinde kullanımı 90 günlük cerrahi alan komplikasyonlarını önlemede etkili bulundu…

The Journal of Arthroplasty 36 (2021) S295–S302

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Revision Arthroplasty

The Effectiveness of Closed-Incision Negative-Pressure Therapy Versus Silver-Impregnated Dressings in Mitigating Surgical Site Complications in High-Risk Patients After Revision Knee Arthroplasty: The PROMISES Randomized Controlled Trial

A B S T R A C T

Background: Revision total knee arthroplasty (rTKA) is associated with significant risk of wound-related morbidity. The present study aimed to evaluate the 1) efficacy of closed-incision negative-pressure therapy (ciNPT) vs silver-impregnated antimicrobial dressing (AMD) in mitigating postoperative surgical site complications (SSCs), 2) the effect of ciNPT vs AMD on certain postoperative health utilization parameters, and on 3) patient-reported outcomes (PROs) improvement at 90-day postoperative follow-up.
Methods: This multicenter randomized controlled trial was conducted between December 2017 and August 2019. Patients ≥22 years, at high risk for SSC, and receiving rTKA with full exchange and reimplantation of new prosthetic components or open reduction and internal fixation of periprosthetic fractures were screened for inclusion. Eligible patients were randomized to receive a commercially available ciNPT system or a silver-impregnated AMD (n = 147, each) for minimum of 5-day duration. Primary outcome was the 90-day incidence of SSCs with stratification in accordance with revision type (aseptic/septic). Secondary outcomes were the 90-day health care utilization parameters (readmission, reoperation, dressing changes, and visits) and PROs.
Results: Of 294 patients randomized (age: 64.9 ± 9.0 years, female: 59.6%), 242 (82.0%) patients completed the study (ciNPT: n = 124; AMD: n = 118). The incidence of 90-day SSCs was lower for the ciNPT cohort (ciNPT: 3.4% vs AMD: 14.3%; odds ratio (OR): 0.22, 95% confidence interval (0.08, 0.59); $P = .0013$). Readmission rates (3.4% vs 10.2%, OR: 0.30(0.11, 0.86); $P = .0208$) and mean dressing changes (1.1 ± 0.3 vs 1.3 ± 1.0; $P = .0003$) were lower with ciNPT. The differences in reoperation rates, number of visits, and PRO improvement between both arms were not statistically significant ($P > .05$).
Conclusion: ciNPT is effective in reducing the 90-day postoperative SSCs, readmission, and number of dressing changes after rTKA. Recommending routine implementation would require true-cost analyses.

International Journal of Surgery 53 (2018) 72–79

Contents lists available at ScienceDirect

International Journal of Surgery

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Review

Negative pressure wound therapy versus conventional wound dressings in treatment of open fractures: A systematic review and meta-analysis

Xi Liu, Hui Zhang*, Shiqiang Cen, Fuguo Huang

The Department of Orthopaedic Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

- Açık kırıklarda NPWT vs klasik cerrahi yara bakımı
- 8 RCT … 421 hasta
- 6 retrospektif çalışma…488 hasta

ABSTRACT

Background: Though several systematic reviews concerned have been published, controversy still exists. The current systematic review was designed to clarify the detailed advantages and disadvantages of the negative pressure wound therapy (NPWT) in treatment of open fractures in comparison with the conventional wound dressings.

Methods: A systematic search was performed in Pubmed, Cochrane Library, Embase, and Google Scholar for the published relevant clinical studies. Unpublished studies were searched in Clinicaltrials, ICTRP and ISRCTN. The outcome measures included presence of infection, wound healing process, length of the patient hospital stay, flap issues, frequency of amputation, and patient life quality.

Results: In the 8 randomized controlled trials (RCTs) (421 patients) and the 6 retrospective cohort studies (488 patients), NPWT resulted in a significantly lower infection rate, significantly shorter wound coverage time, wound healing time and hospital stay length, and the lower amputation rate. However, no statistically significant difference was found in the need for flap surgery, the proportion of free flaps, the flap failure rate or the fracture non-union rate. Only 1 RCT was reported to have a higher physical component score of short form 36 in the infected patients.

Conclusion: NPWT can significantly reduce the risk of infection in treatment of open fractures and accelerate their wound healing process. Some but not much evidence suggests that NPWT may possibly help reduce the severity of the limb injury and therefore provide a chance for the limb to avoid amputation. Use of NPWT in the flap area is probably safe, but should be carried out with caution. The advantage of NPWT over the conventional wound dressings still requires to be confirmed in the other aspects.

NPWT lehine…

- Enfeksiyon görülme oranı
- Hastanede yatış süresi
- İkincil amputasyon oranı

Fark görülmeyenler…

- Flap cerrahisi ihtiyacı
- Flap başarısızlığı
- Non-union oranı

Sonuç- NPWT enfeksiyonu önlemek ve yara iyileşmesini hızlandırmak amaçlı kullanılabilir

International Journal of Surgery 76 (2020) 94–100

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Review

A systematic review and meta-analysis comparing the effectiveness of negative-pressure wound therapy to standard therapy in the prevention of complications after vascular surgery

Fiona Sexton, Donagh Healy*, Stephen Keelan, Mohammed Alazzawi, Peter Naughton

Dept. Vascular Surgery, Beaumont Hospital, Dublin, Ireland

ABSTRACT

Introduction: Negative pressure wound therapy (NPWT) dressings reduce wound complications in a variety of settings but it is unclear whether they reduce groin wound complications in closed incisions after vascular surgery. Therefore, we performed a systematic review and meta-analysis.

Methods: Randomised controlled trials on the use of negative pressure wound dressings on closed groin incisions following vascular surgery were identified from an electronic search of abstract databases, conference proceedings and article reference lists. The primary outcome was surgical site infection (SSI) and secondary outcomes were seromas, readmissions within 30 days postoperatively, reoperations and length of stay.

Results: 7 exploratory trials involving 935 incisions and an unclear number of patients were identified. 4 trials yielded primary outcome results that favoured NPWT. Meta-analysis found that NPWT dressings reduced SSIs (RR 0.47; 95%CI 0.31–0.70; 3 studies, 422 patients). No other meta-analyses could be performed.

Conclusion: NPWT dressings are a promising intervention that may reduce the incidence of groin wound complications following vascular surgery. However, further large-scale well-designed studies are needed before NPWT dressings can become the standard of care.

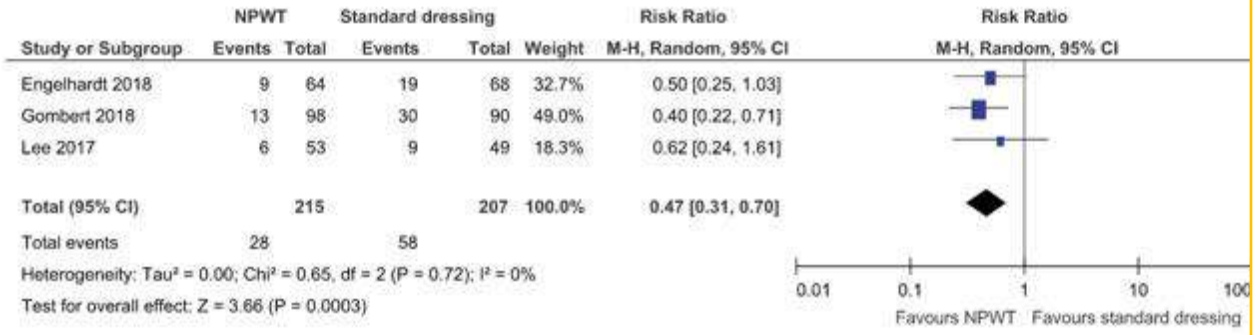


Fig. 2. Forest plot for the outcome of surgical site infection.

- Vasküler cerrahi sonrası NPWT vs standart yara bakımı
- 7 RCT çalışma…935 insizyon uygulaması
- Cerrahi alan infeksiyonu, seroma, 30 gün içinde hastaneye yatış gerektiren başvuru veya ameliyat
- 4 çalışmanın sonuçları NPWT lehine
- En belirgin fark infeksiyon oluşumunun önlenmesi…

Cochrane Library

Cochrane Database of Systematic Reviews

Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus (Review)

Liu Z, Dumville JC, Hinchliffe RJ, Cullum N, Game F, Stubbs N, Sweeting M, Peinemann F

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of partici-pants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with placebo	Risk with NPWT compared with dressings				
Proportion of wounds healed Follow-up: 16 weeks	Study population 388 per 1000	559 per 1000 (400 to 780)	**RR 1.44** (1.03 to 2.01)	162 (1 study)	⊕⊕◯◯ **Low**[a,b]	—
Time to healing Follow-up: 16 weeks	Study population 388 per 1000	609 per 1000 (448 to 770)	**HR 1.91** (1.21 to 2.99)	162 (1 study)	⊕⊕◯◯ **Low**[a,b]	—
Amputations Follow-up: 16 weeks or unspecified	Study population 60 per 1000	23 per 1000 (8 to 61)	**RR 0.38** (0.14 to 1.02)	292 (2 studies)	⊕◯◯◯ **Very low**[a,c]	—
Number of wounds closed or covered with surgery	954 per 1000	1000 per 1000 (238 to 1000)	**RR 1.02** (0.95 to 1.09)	130 (1 study)	⊕◯◯◯ **Very low**[a,c]	—
Adverse events Follow-up: 16 weeks	Study population 541 per 1000	520 per 1000 (390 to 693)	**RR 0.96** (0.72 to 1.28)	162 (1 study)	⊕◯◯◯ **Very low**[a,c]	—
Cost-effectiveness	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	—
Wound recurrence	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	—

- Toplam RCT 11 çalışma, toplam 972 kişi
- Çalışma popülasyonları; 15 …341 arası
- 75-125 mmHg basınç aralığı …

DM hastada post op yarada standart tedavi vs NPWT

16 hf takip

- İyileşmeye etkisi (+)
- İyileşme hızına etkisi (+)
- Tam kapanma veya cerrahi ile tam kapanma NPWT lehine
- Yan etki düşük
- Maliyet etkinlik?
- Yara rekürrens ?

Kanıt düzeyi düşük ek RCT çalışma lazım

Liu Z, Dumville JC, Hinchliffe RJ, Cullum N, Game F, Stubbs N, Sweeting M, Peinemann F. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database Syst Rev. 2018 Oct 17;10(10):CD010318. doi: 10.1002/14651858.CD010318.pub3. PMID: 30328611; PMCID: PMC6517143.

Summary of findings 2. NPWT compared with dressings for foot ulcers in people with diabetes mellitus

NPWT compared with dressings for diabetic foot ulcers

Patient or population: treating foot wounds in people with diabetes mellitus

Setting: hospital

Intervention: NPWT

Comparison: dressings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with NPWT compared with dressings			
Proportion of wounds healed Follow-up: unclear for 4 studies and 8–16 weeks for the other 3 studies	Study population		**RR 1.40** (1.14 to 1.72)	486 (5 studies)	⊕⊕◯◯ **Low**[a,b]
	406 per 1000	540 per 1000 (475 to 617)			
Time to healing Follow-up: unclear for 2 studies and 16 weeks for the other study	Study population		—	468 (3 studies)	⊕⊕◯◯ **Low**[a,b]
	See comment	See comment			
Amputations Follow-up: unclear for 4 studies and 16 weeks for the other study	Study population		**RR 0.33** (0.15 to 0.70)	441 (3 studies)	⊕⊕◯◯ **Low**[a,b]
	114 per 1000	38 per 1000 (17 to 80)			
Number of wounds closed or covered with surgery Follow-up: unclear	Study population		**RR 1.02** (0.85 to 1.24)	129 (3 studies)	⊕⊕◯◯ **Low**[a,b]
	714 per 1000	729 per 1000 (607 to 886)			
Adverse events	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Cost-effectiveness	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Wound recurrence Follow-up: 6–10 months	Study population		**RR 0.50** (0.10 to 2.53)	60 (1 study)	⊕◯◯◯ **Very low**[a,c]
	133 per 1000	66 per 1000 (12 to 297)			

DM ayak yarasında tedavide standart tedavi vs NPWT

8-16 hf takip (ortalama)

- İyileşmeye etkisi (+)
- İyileşme hızına etkisi ?
- Amputasyon oranı NPWT lehine düşük
- Tam kapanma veya cerrahi ile tam kapanma NPWT lehine
- Yan etki?
- Maliyet etkinlik?
- Yara rekürrens…6-10 aylık takipte NPWT lehine

Kanıt düzeyi düşük ek RCT çalışma lazım

Liu Z, Dumville JC, Hinchliffe RJ, Cullum N, Game F, Stubbs N, Sweeting M, Peinemann F. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database Syst Rev. 2018 Oct 17;10(10):CD010318. doi: 10.1002/14651858.CD010318.pub3. PMID: 30328611; PMCID: PMC6517143.

Summary of findings 3. Low-pressure compared with high-pressure NPWT for foot ulcers in people with diabetes mellitus

Low-pressure compared with high-pressure NPWT for diabetic foot ulcers

Patient or population: treating foot wounds in people with diabetes mellitus

Setting: hospital

Intervention: low-pressure NPWT (75 mmHg)

Comparison: high-pressure NPWT (125 mmHg)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with low compared with high pressure of NPWT			
Proportion of wounds healed	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Time to ulcer healing	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Amputation	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Number of wounds closed or covered with surgery Follow-up: 4 weeks	Study population		**RR 0.83** (0.47 to 1.47)	40 (1 study)	⊕◯◯◯ **Very low**[a]
	600 per 1000	498 per 1000 (282 to 882)			
Adverse events Follow-up: 4 weeks	Study population		**RR 1.50** (0.28 to 8.04)	40 (1 study)	⊕◯◯◯ **Very low**[a]
	100 per 1000	150 per 1000 (28 to 804)			
Cost-effectiveness	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Wound recurrence	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable

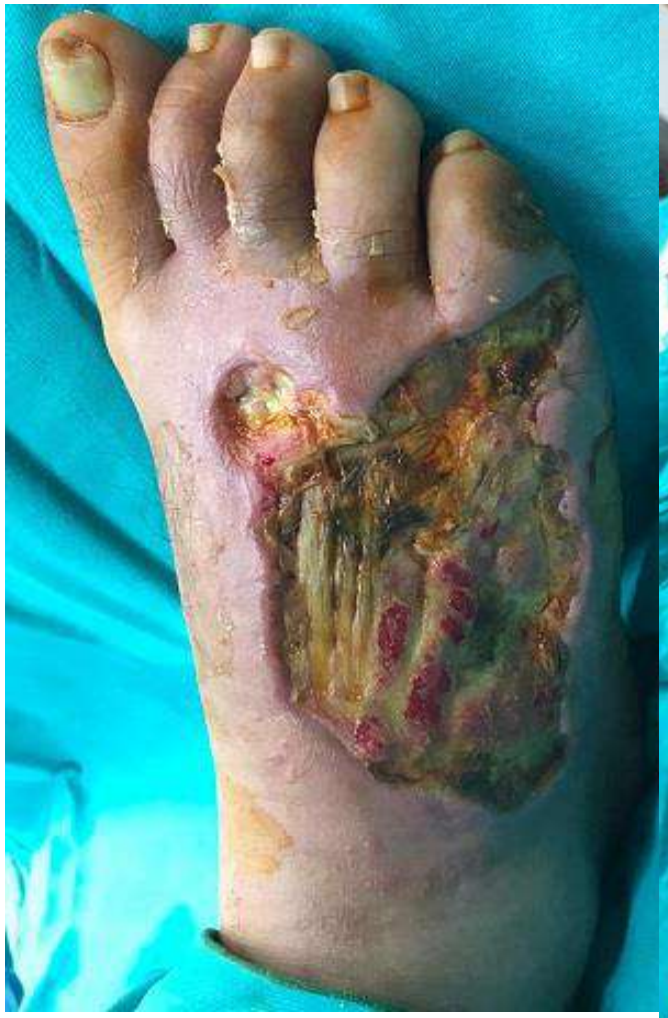
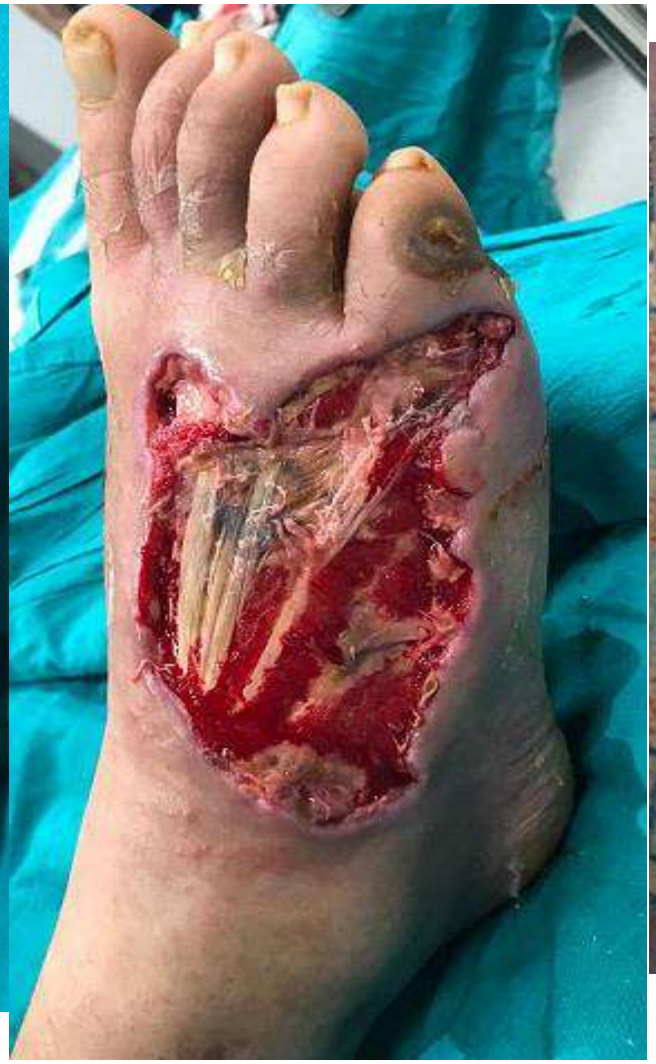
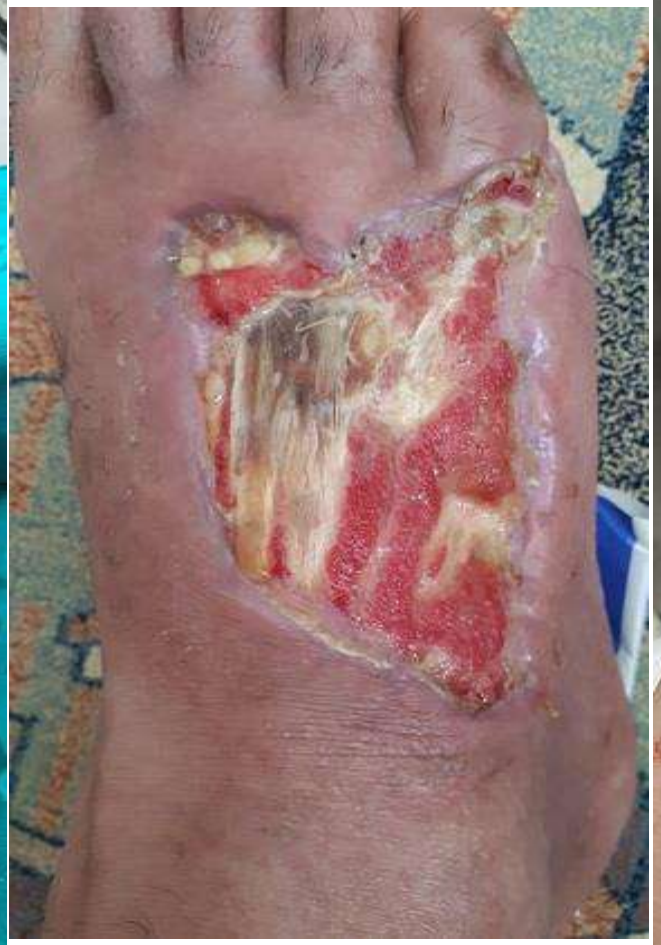
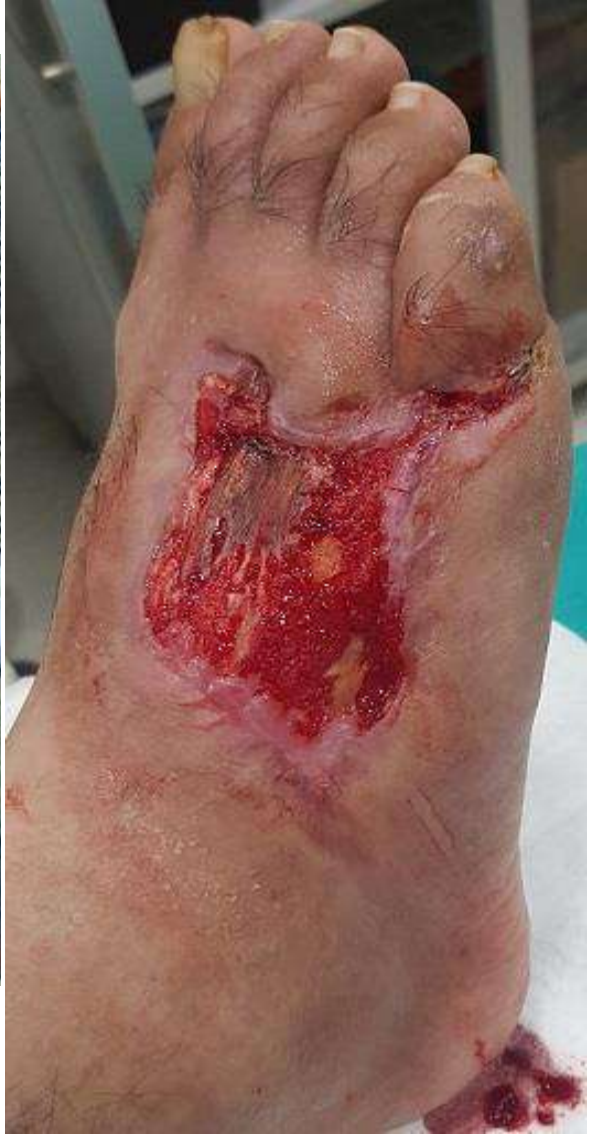
NPWT, DM ayak ülserlerinde düşük basınç (-75mmHg) ve yüksek basınç (-125mmHg) kıyaslaması…

4 hf takip

- Farklı basınç iyileşmeye etkisi?
- Farklı basınç iyileşme hızına etkisi ?
- Farklı basınç amputasyon oranı ?
- Tam kapanma veya cerrahi ile tam kapanma düşük basınç lehine
- Yan etki fazla düşük basınç lehine
- Maliyet etkinlik?
- Yara rekürrens?

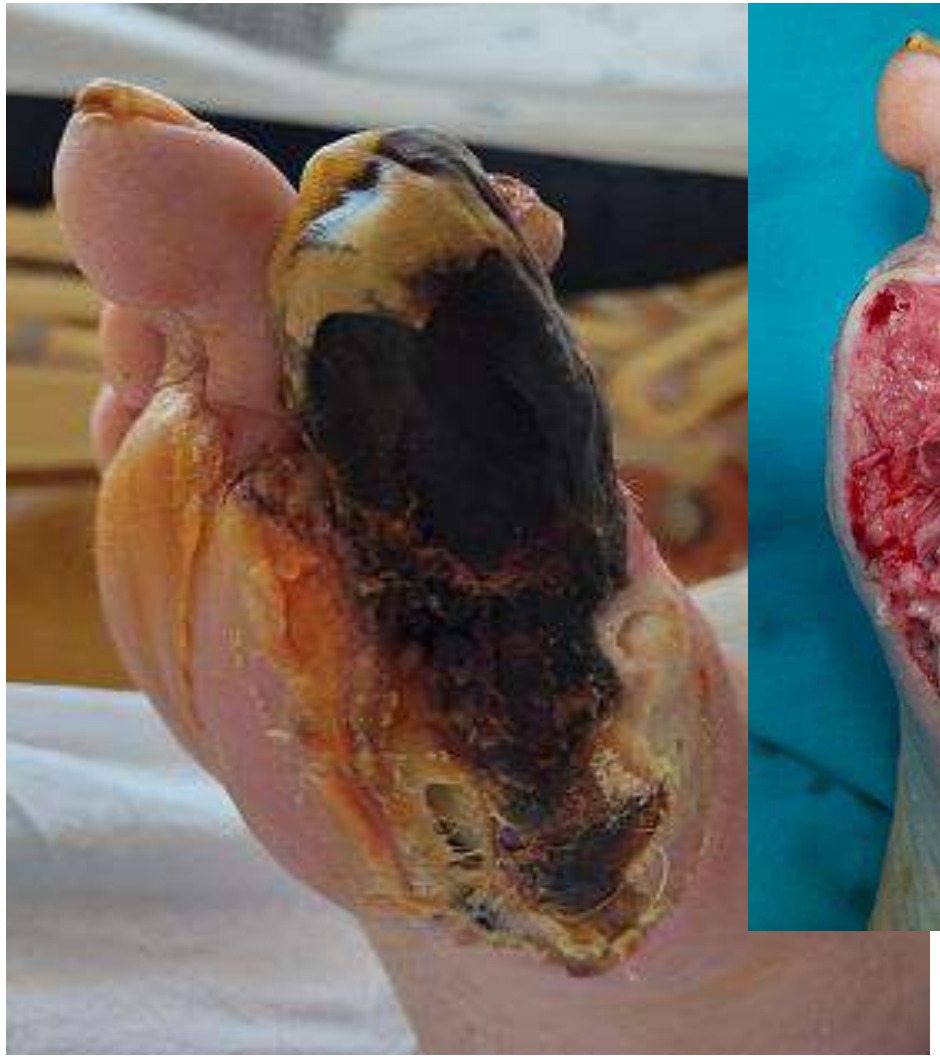
Kanıt düzeyi düşük ek RCT çalışma lazım

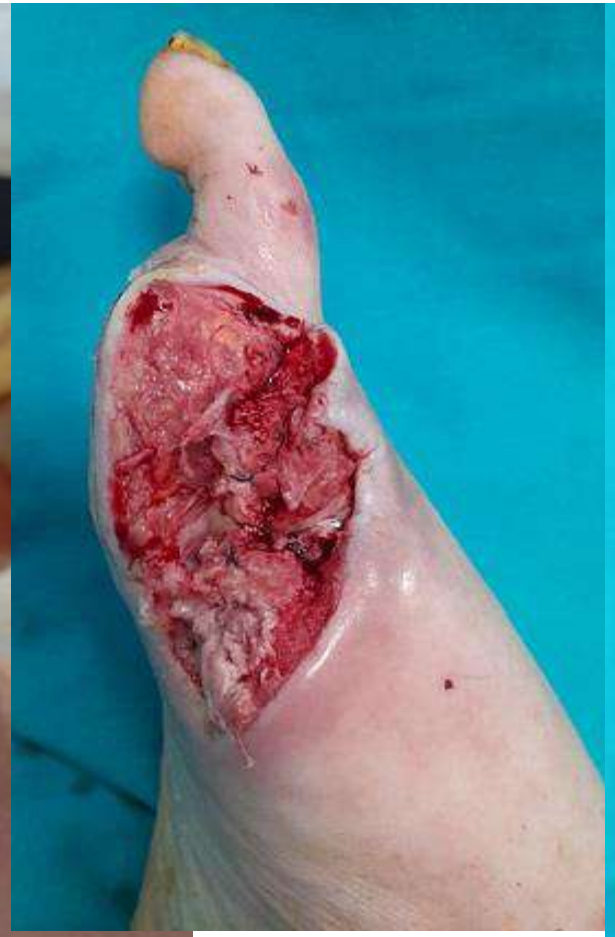
Liu Z, Dumville JC, Hinchliffe RJ, Cullum N, Game F, Stubbs N, Sweeting M, Peinemann F. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database Syst Rev. 2018 Oct 17;10(10):CD010318. doi: 10.1002/14651858.CD010318.pub3. PMID: 30328611; PMCID: PMC6517143.

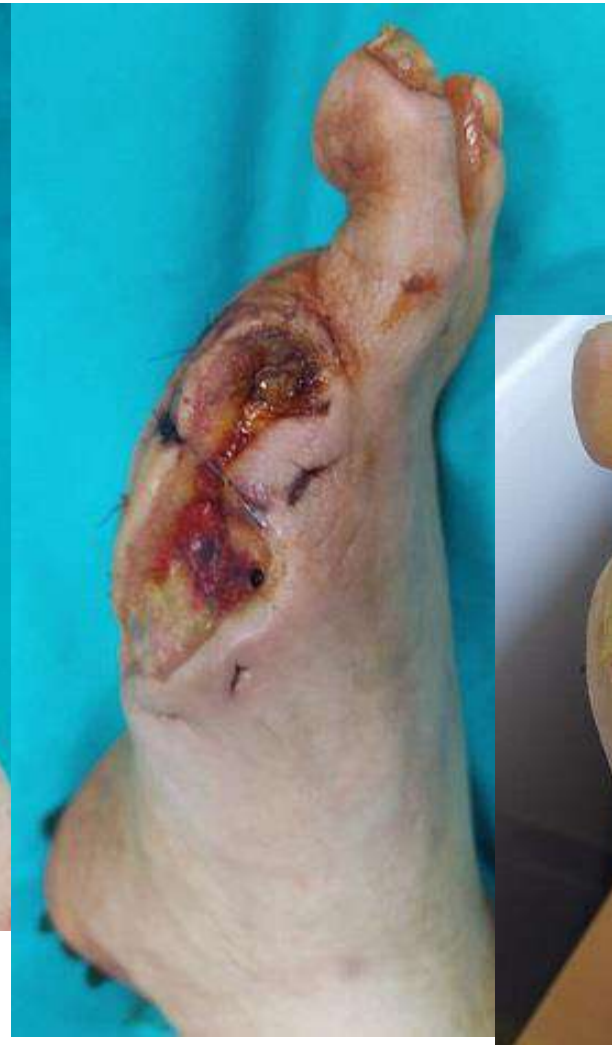





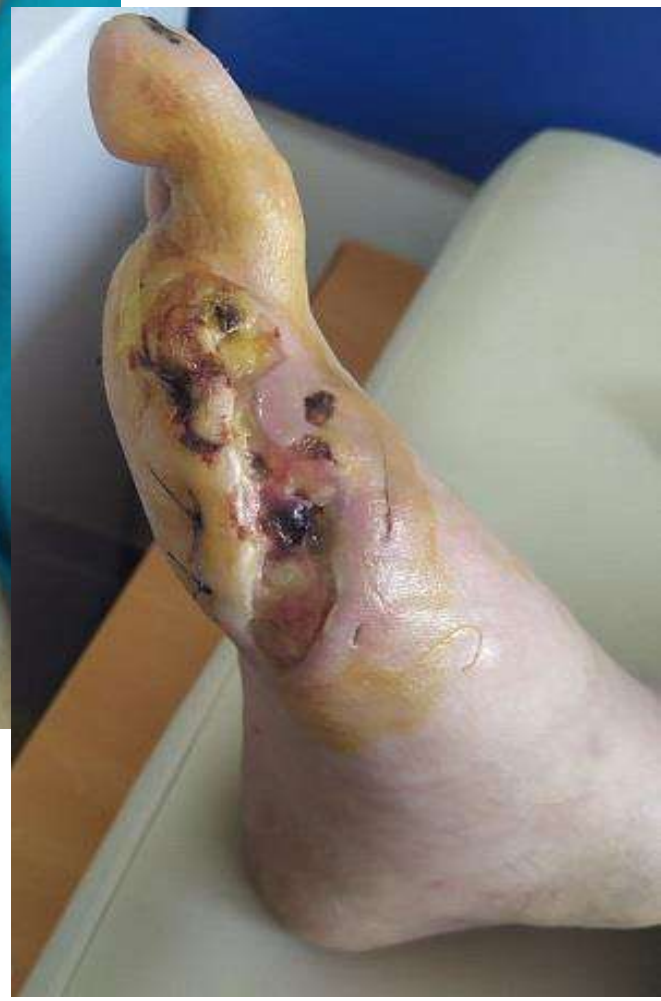
6 seans Gümüşlü VAC, -120 mmHg

Doç.Dr.Bayram ÇOLAK ile CONFORT Çalışması



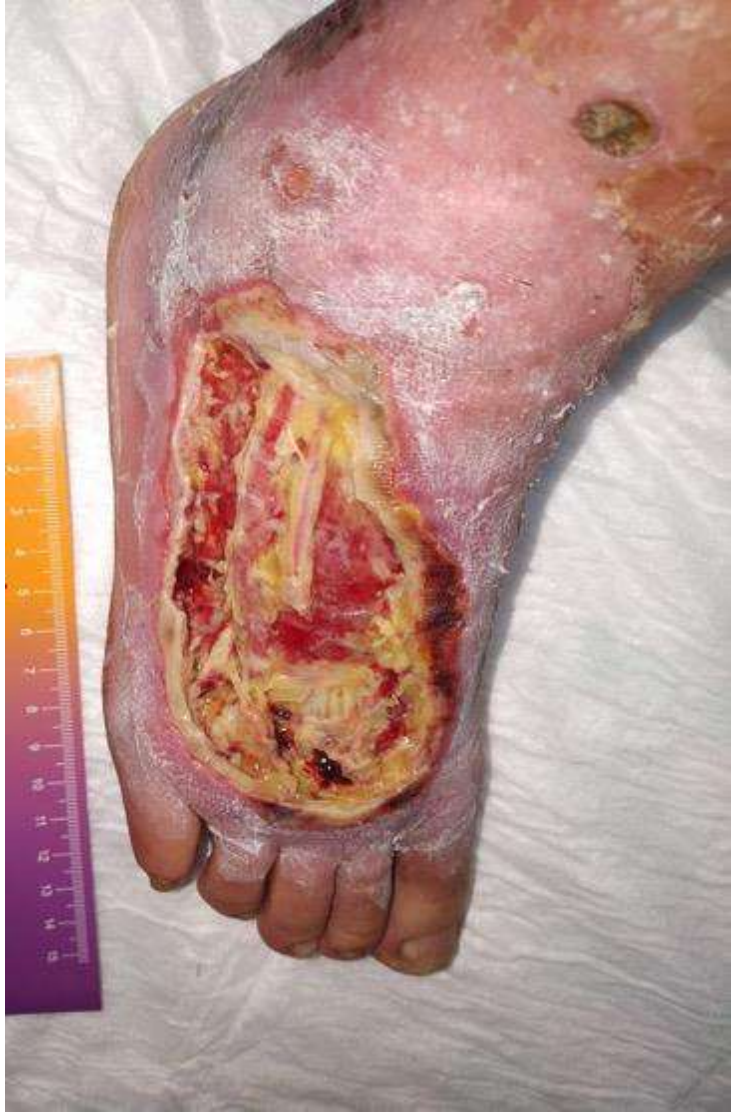


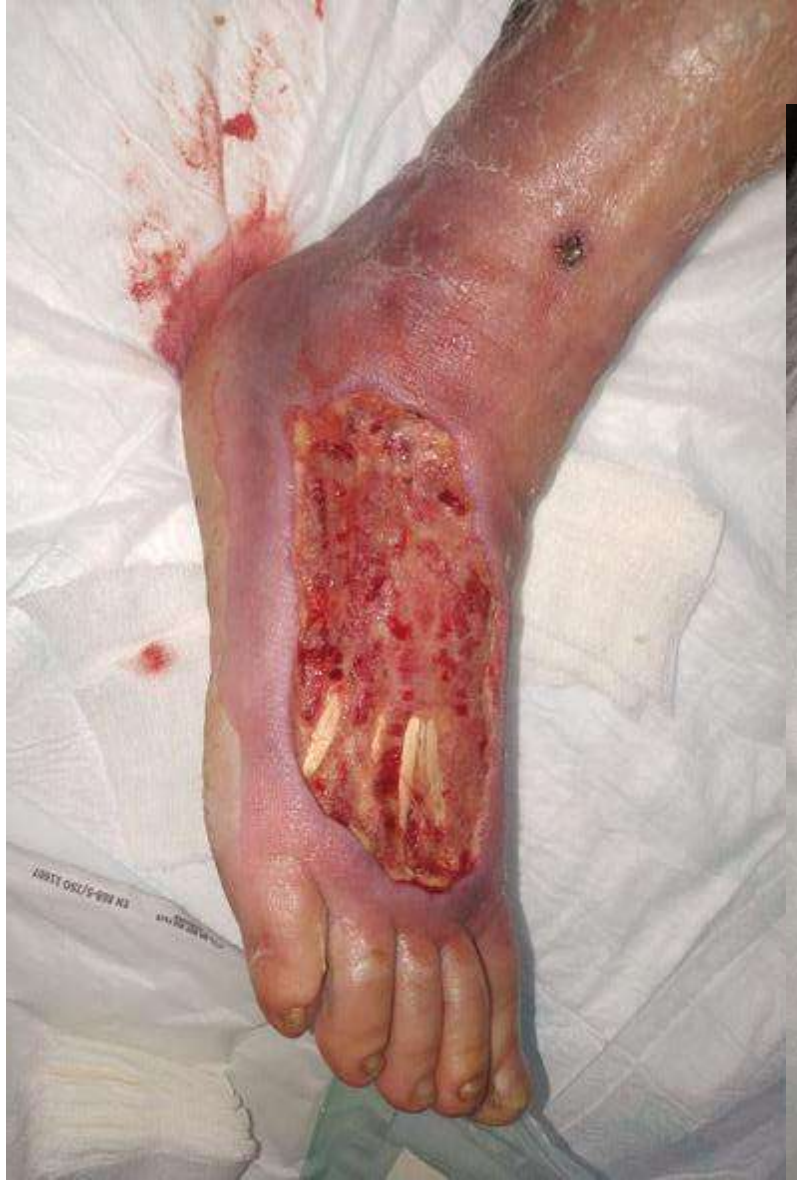


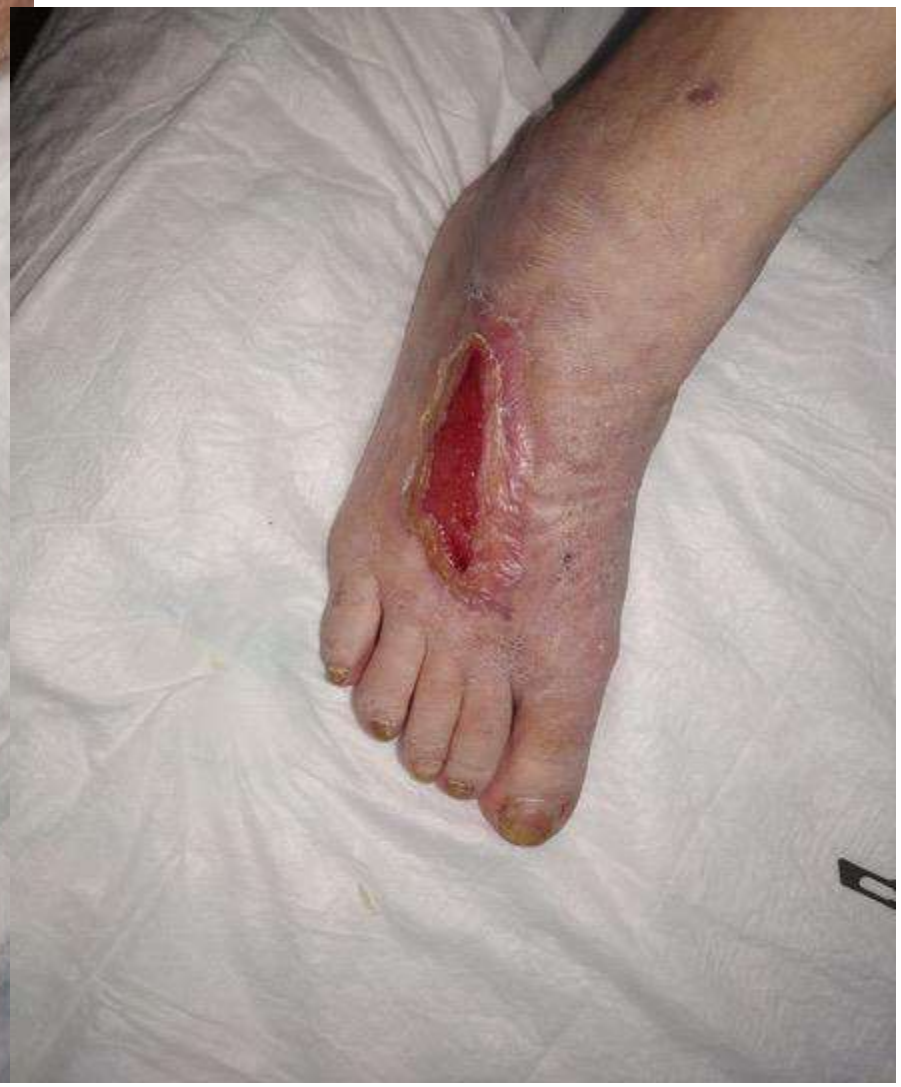


6 seans Gümüşlü VAC, -120 mmHg

Doç.Dr.Bayram ÇOLAK ile CONFORT Çalışması



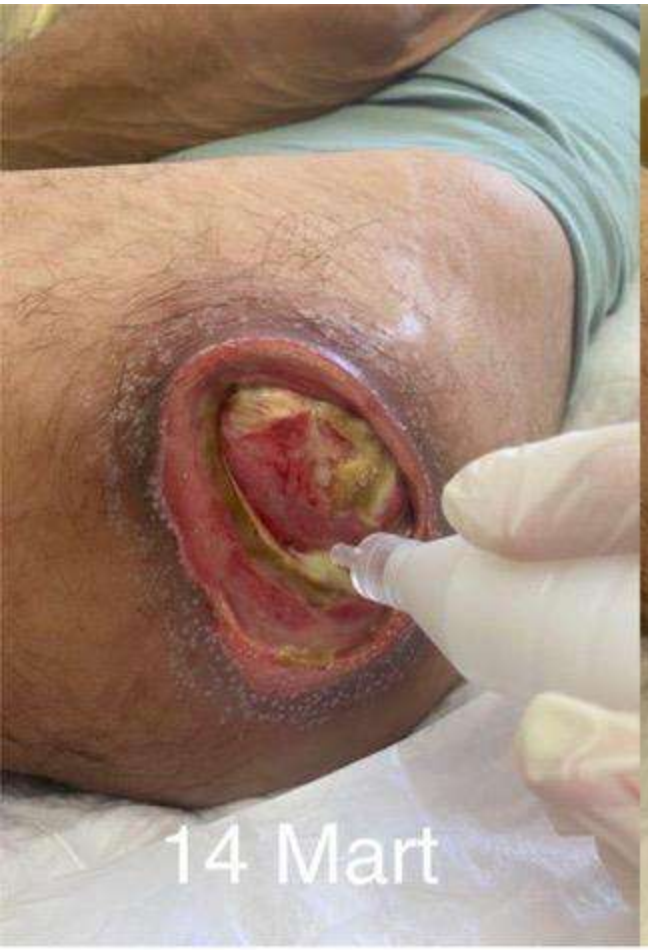




4 seans Gümüşlü VAC, -120 mmHg

Uzm.Dr.Nihal GÜNEŞ ile CONFORT Çalışması

Soğuk Atmosferik Plazma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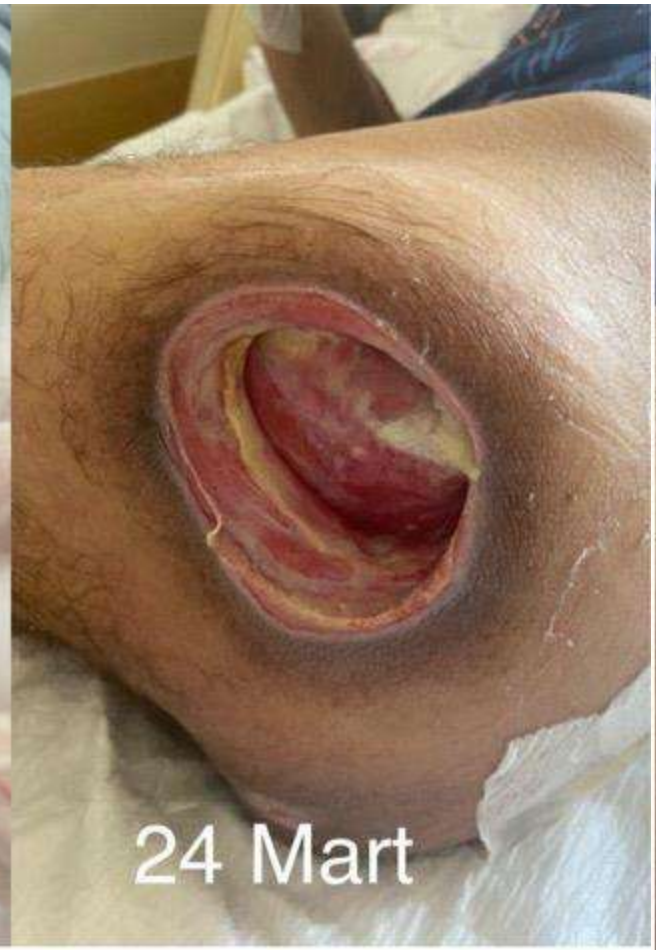
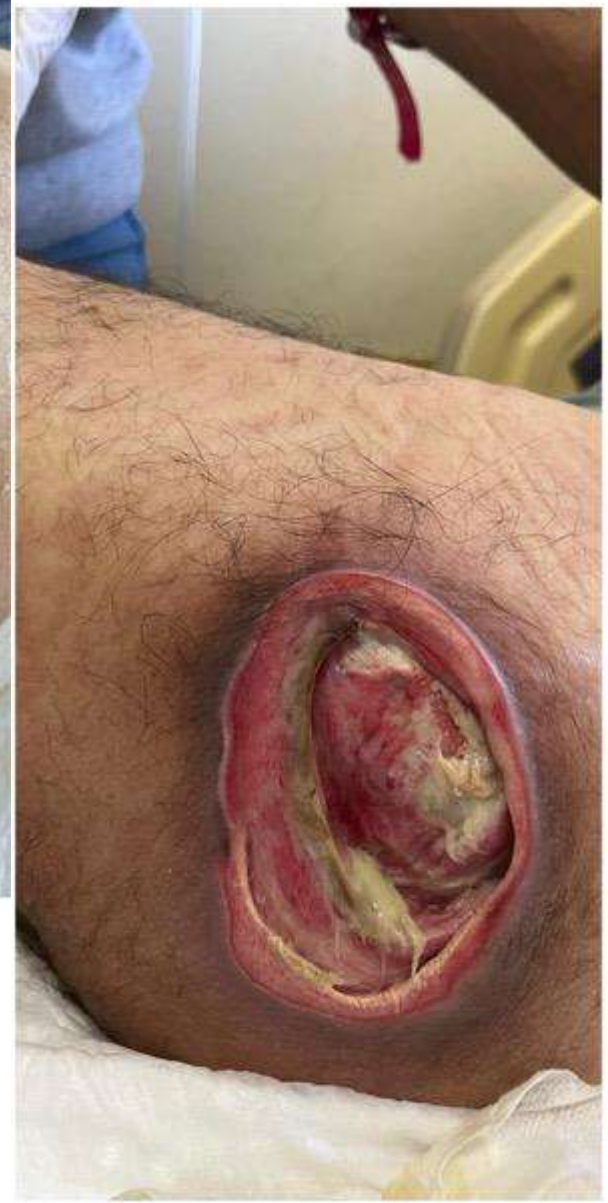
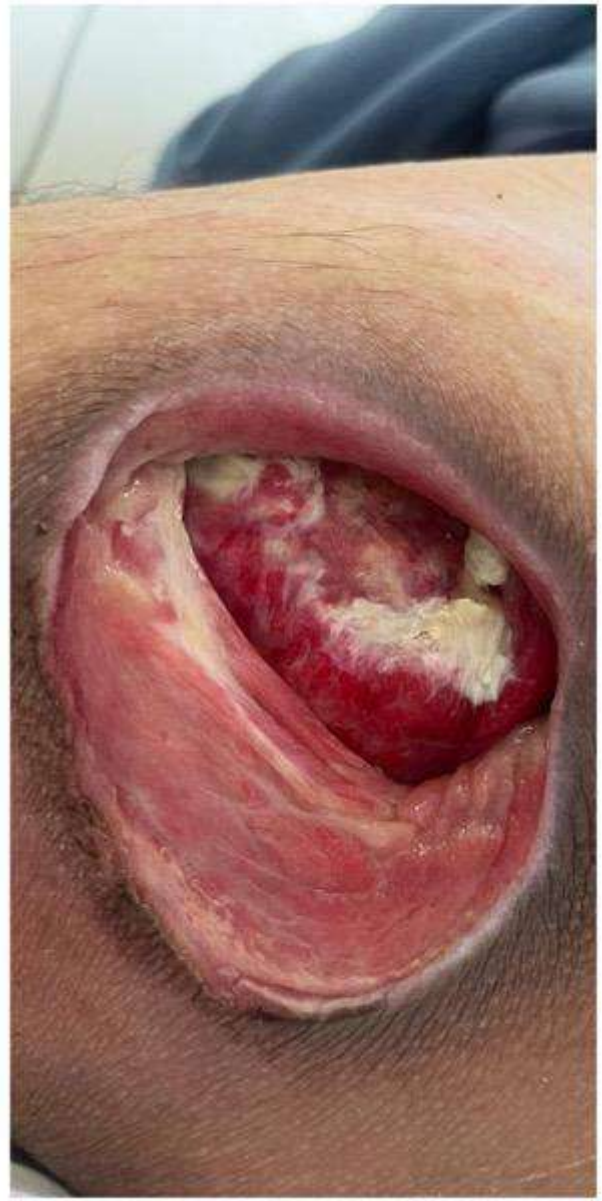
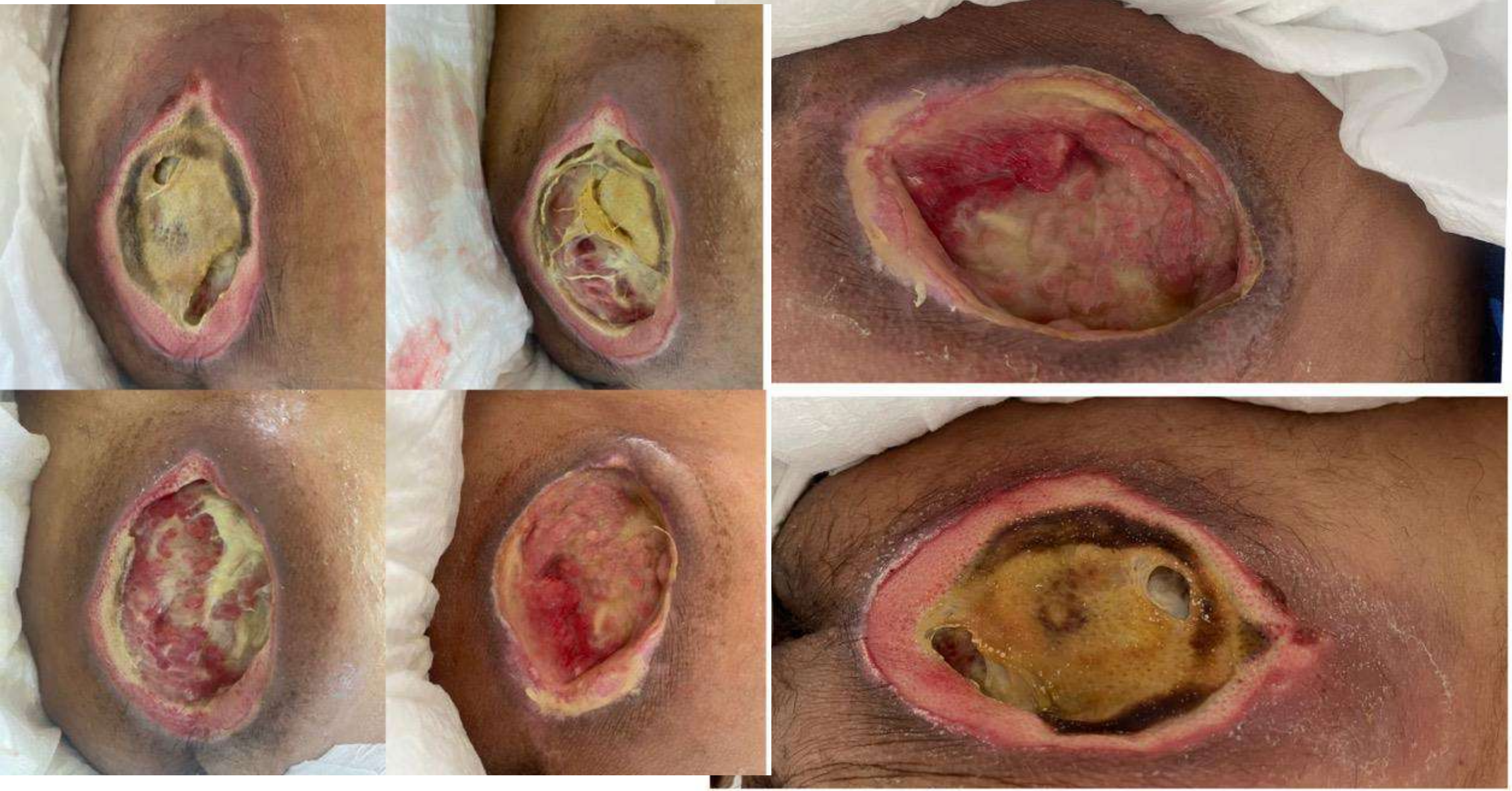
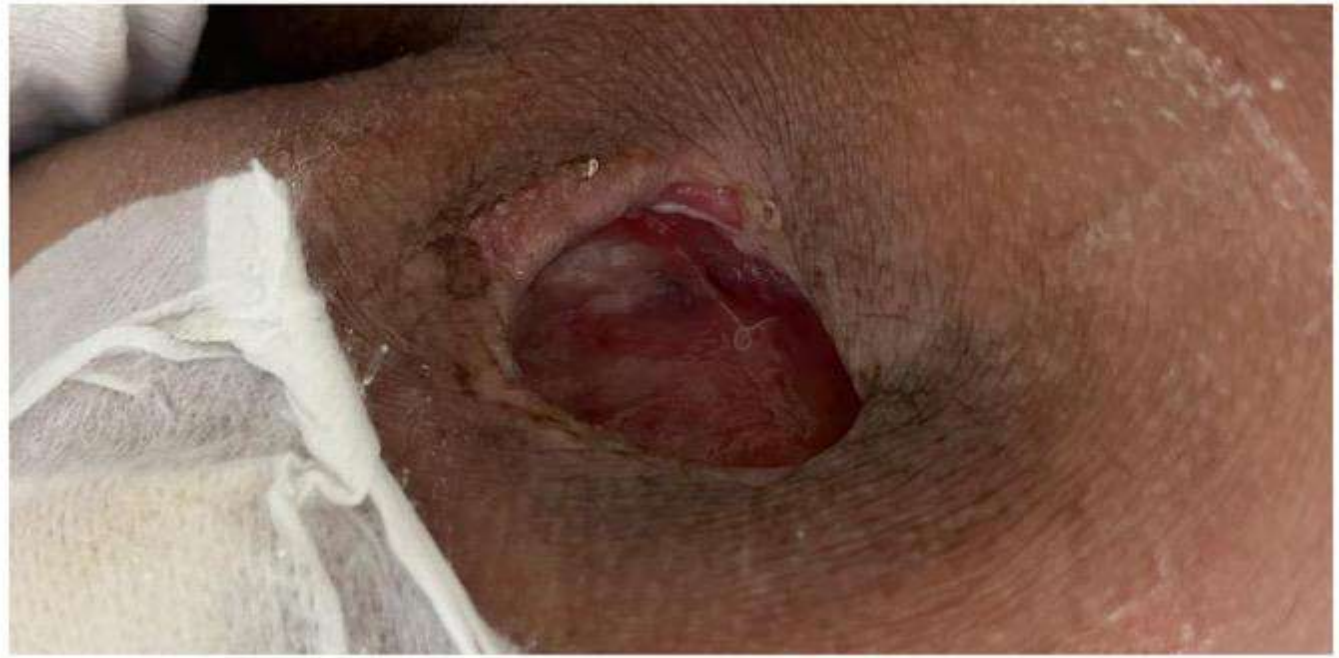
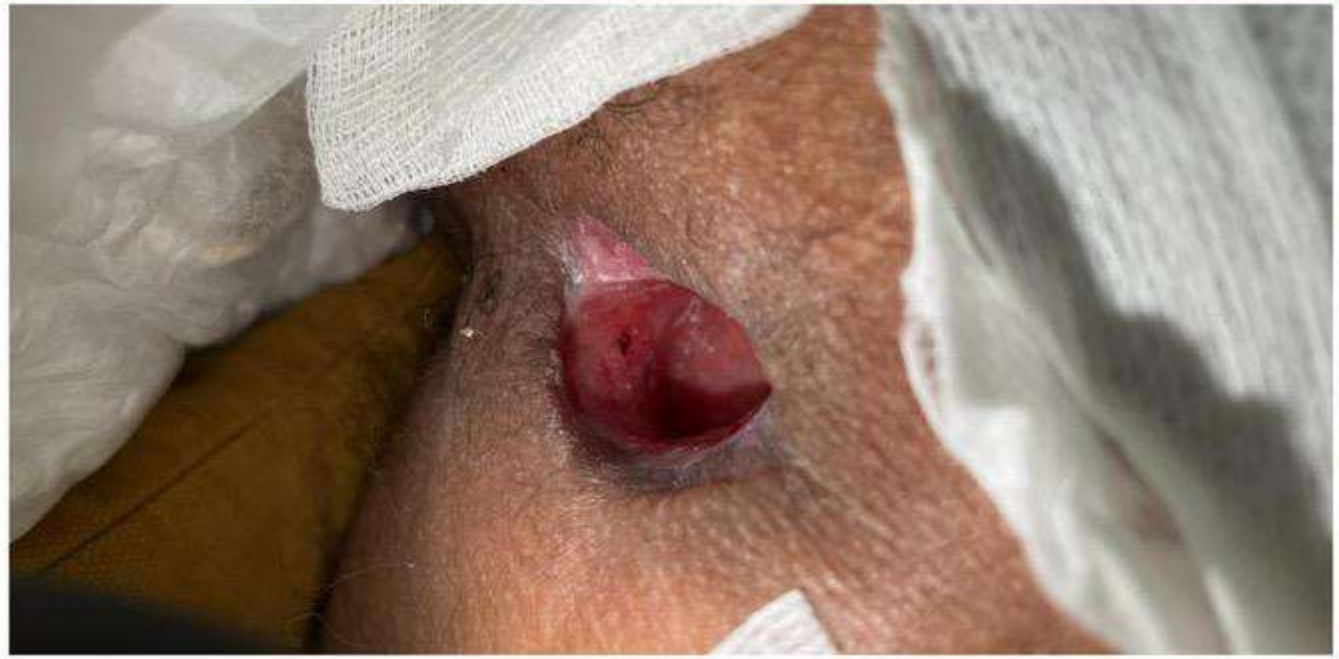

24 Mart



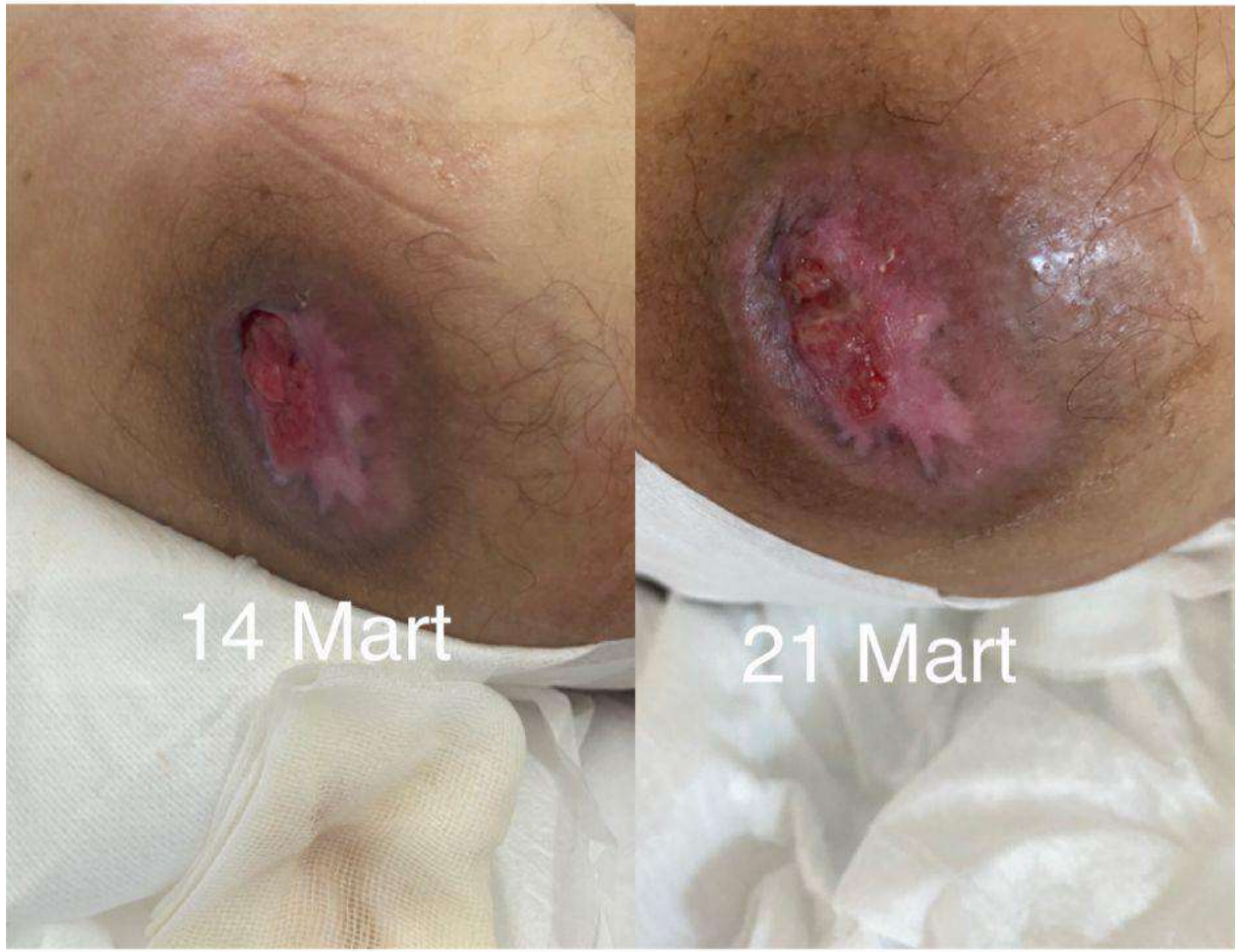


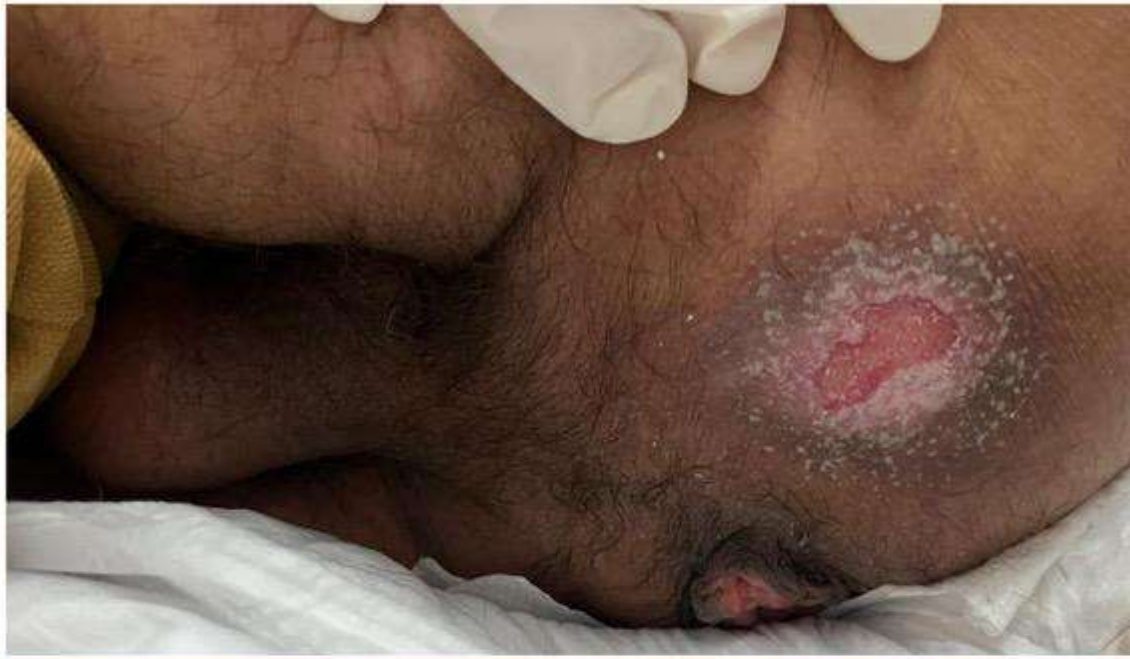


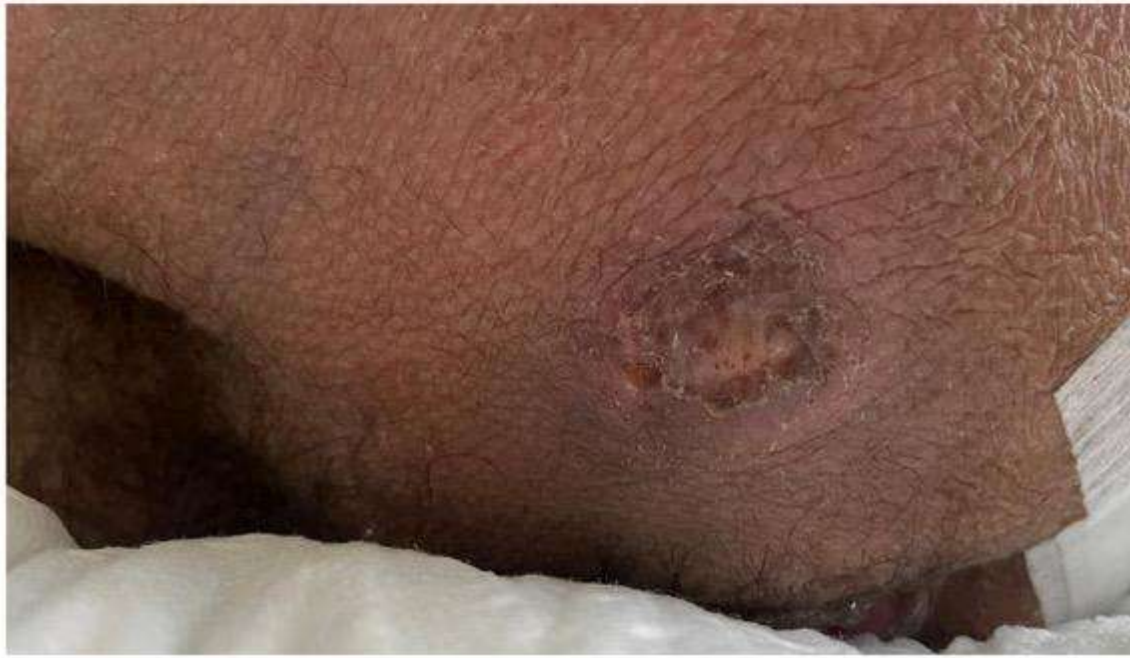




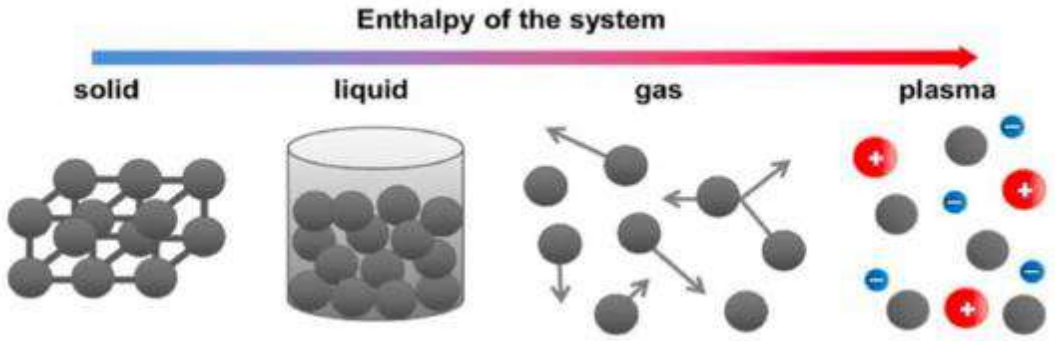

14 Mart
21 Mart


14 Mart
21 Mart





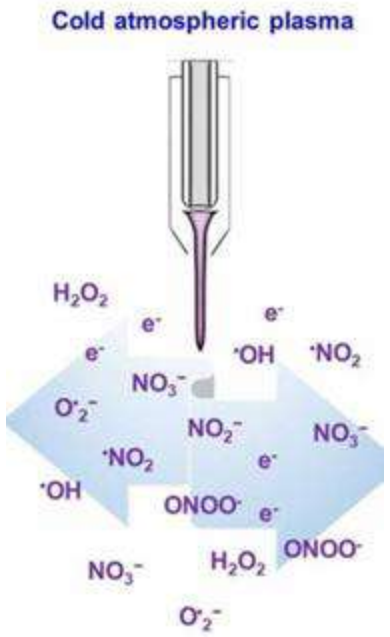
Katı-sıvı-gaz-plazma



Güneşte

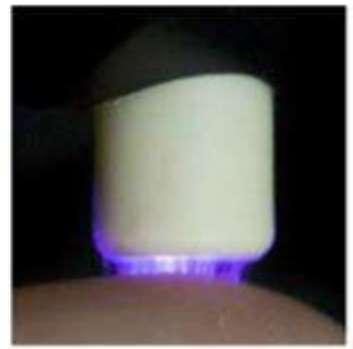
Şimşekte

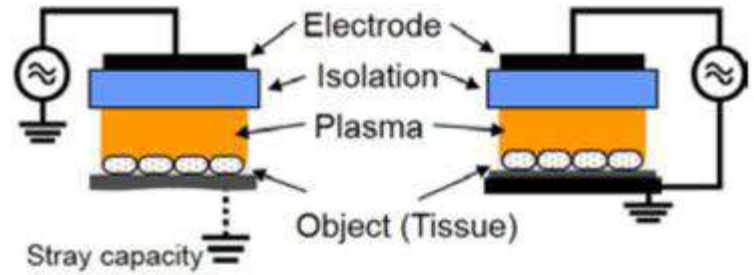
- Sıcak plazma=4000C
- Soğuk plazma=30-50C



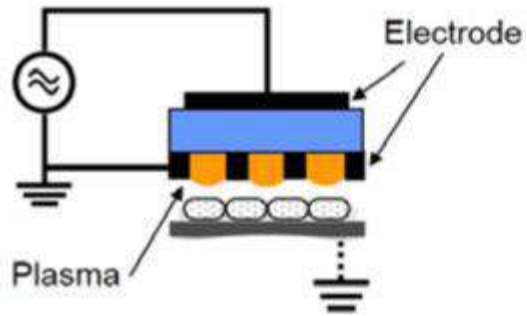
- Havadan O_2 ve N_2 serbest radikaller
- Maddeyi iyonlarına ayırır

Volume dielectric barrier discharge (DBD)

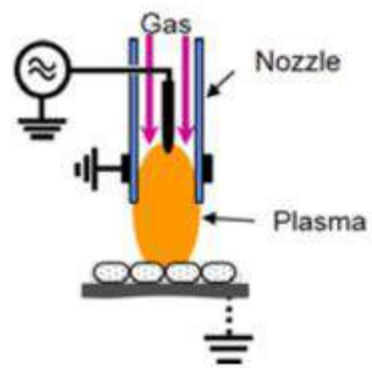


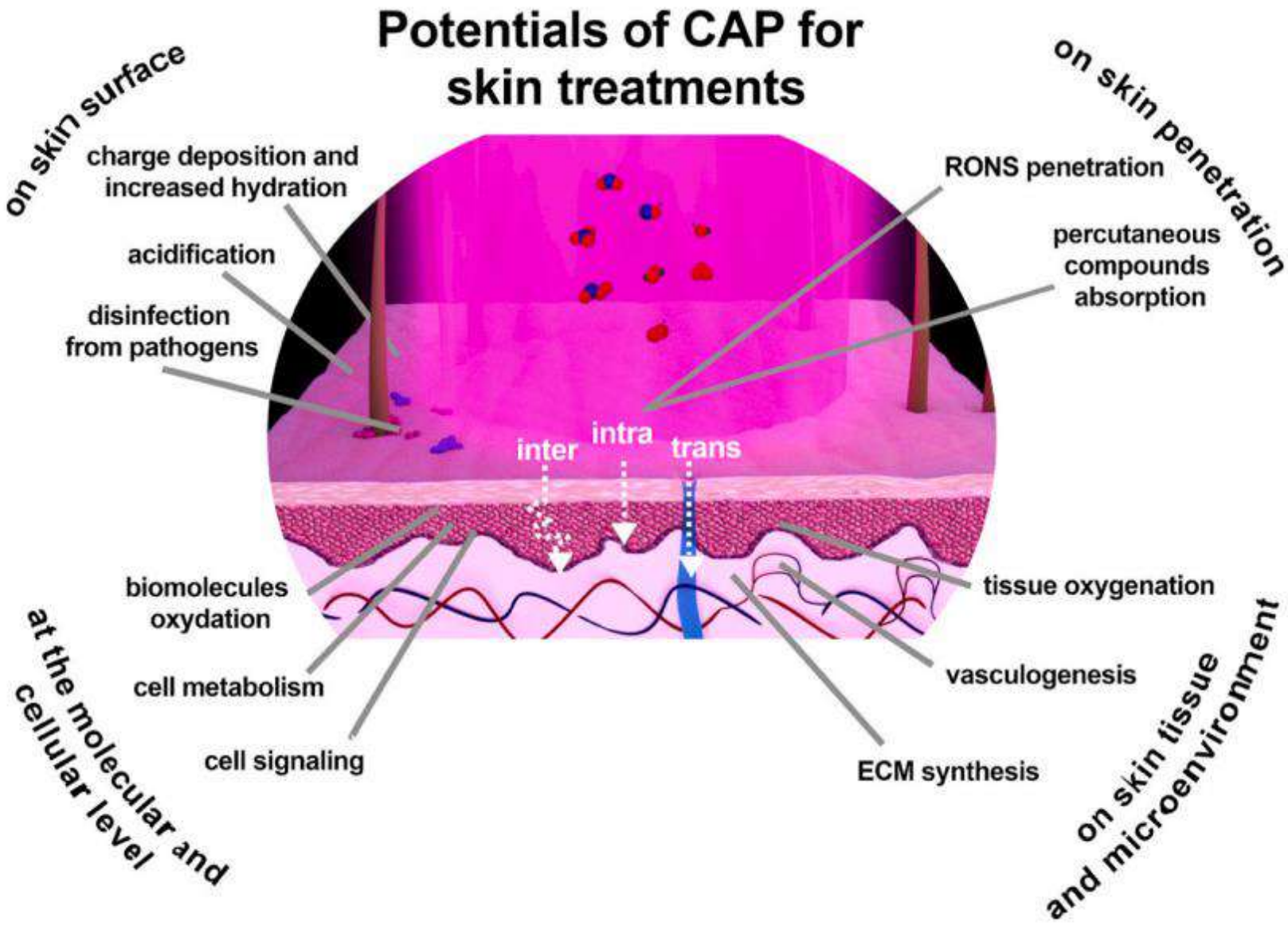


Surface dielectric barrier discharge (DBD)

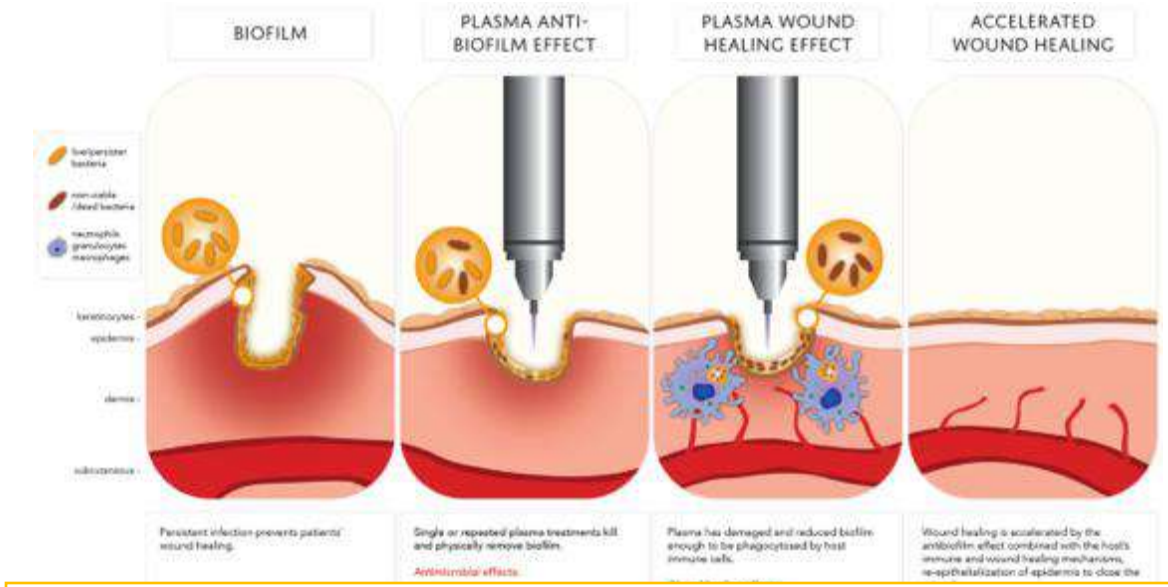


Plasma jet





Giovanni Busco, Eric Robert, Nadira Chettouh-Hammas, Jean-Michel Pouvesle, Catherine Grillon,The emerging potential of cold atmospheric plasma in skin biology, Free Radical Biology and Medicine,Volume 161,2020,Pages 290-304



- Anti bakteriyel etki
- Biyofilm parçalayıcı etki
- ROS=reaktif oksijen radikalleri
- RNS=reaktif azot radikalleri
- Anjiyogenesis
- Keratinosit göçü artışı
- Büyüme faktörü artışı
- Sitokin dengesi- M2 makrofaj aktivitesi artışı

ROS RNS

Kısa ömürlü partiküller
- Tek oksijen
- Süperoksit anyonlar
- Peroksinitrit
- Hidroksi radikaller

Uzun ömürlü partiküller
- Hidrojen peroksit
- Nitritler
- Nitratlar

Doz bağımlı sonuçlar

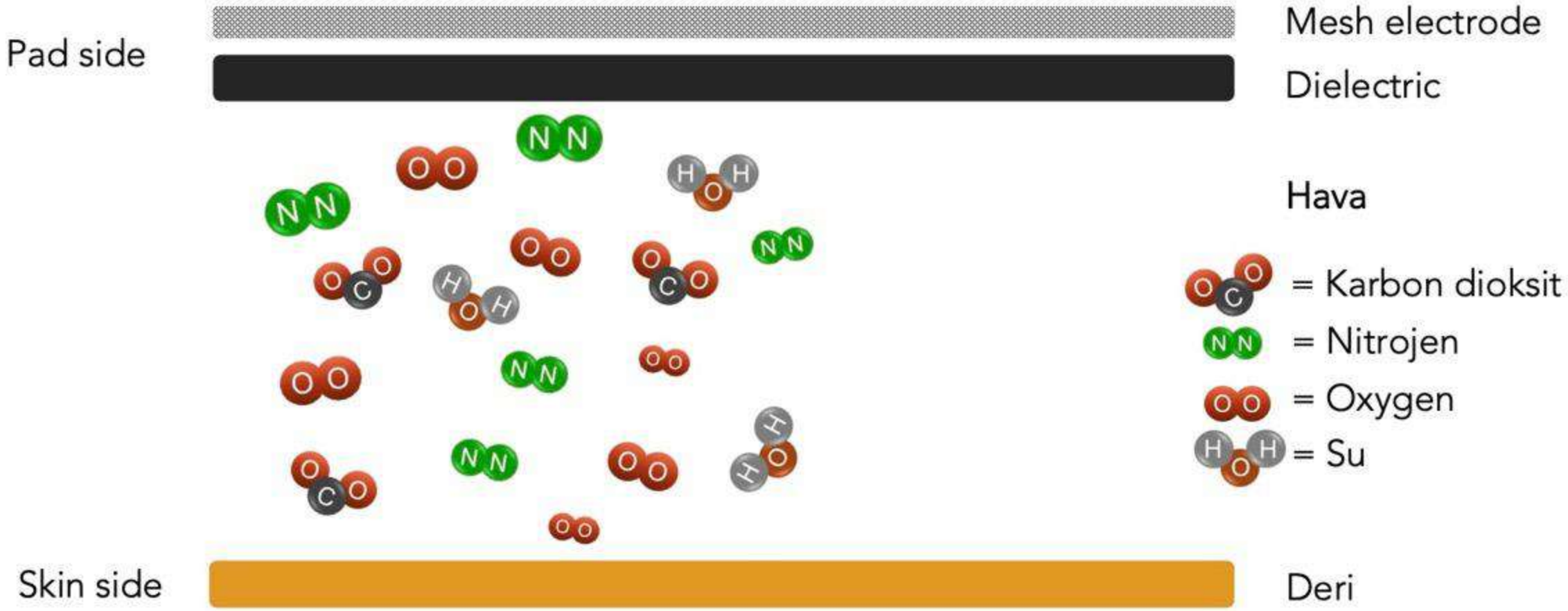
Düşük doz
- Hücre siklüsü durması
- Otofaji
- Biyolojik yaşlanma

Yüksek doz
- Hücre nekrozu
- Hücre ölümü

Bolgeo, T.; Maconi, A.; Gardalini, M.; Gatti, D.; Di Matteo, R.; Lapidari, M.; Longhitano, Y.; Savioli, G.; Piccioni, A.; Zanza, C. The Role of Cold Atmospheric Plasma in Wound Healing Processes in Critically Ill Patients. *J. Pers. Med.* **2023**, *13*, 736. https://doi.org/10.3390/jpm13050736

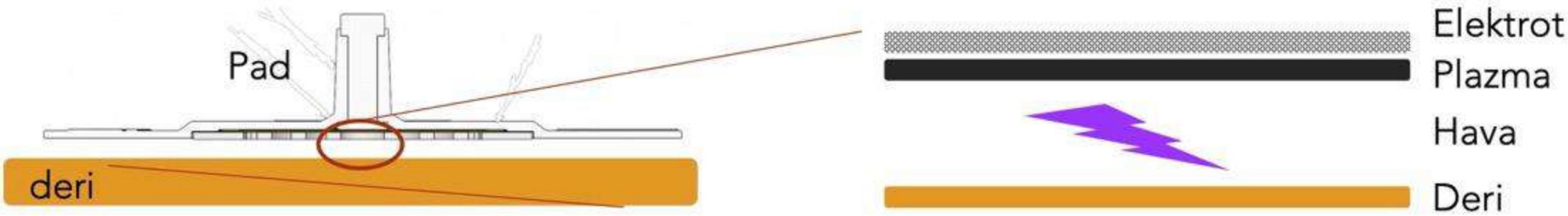
Çalışma Methodu

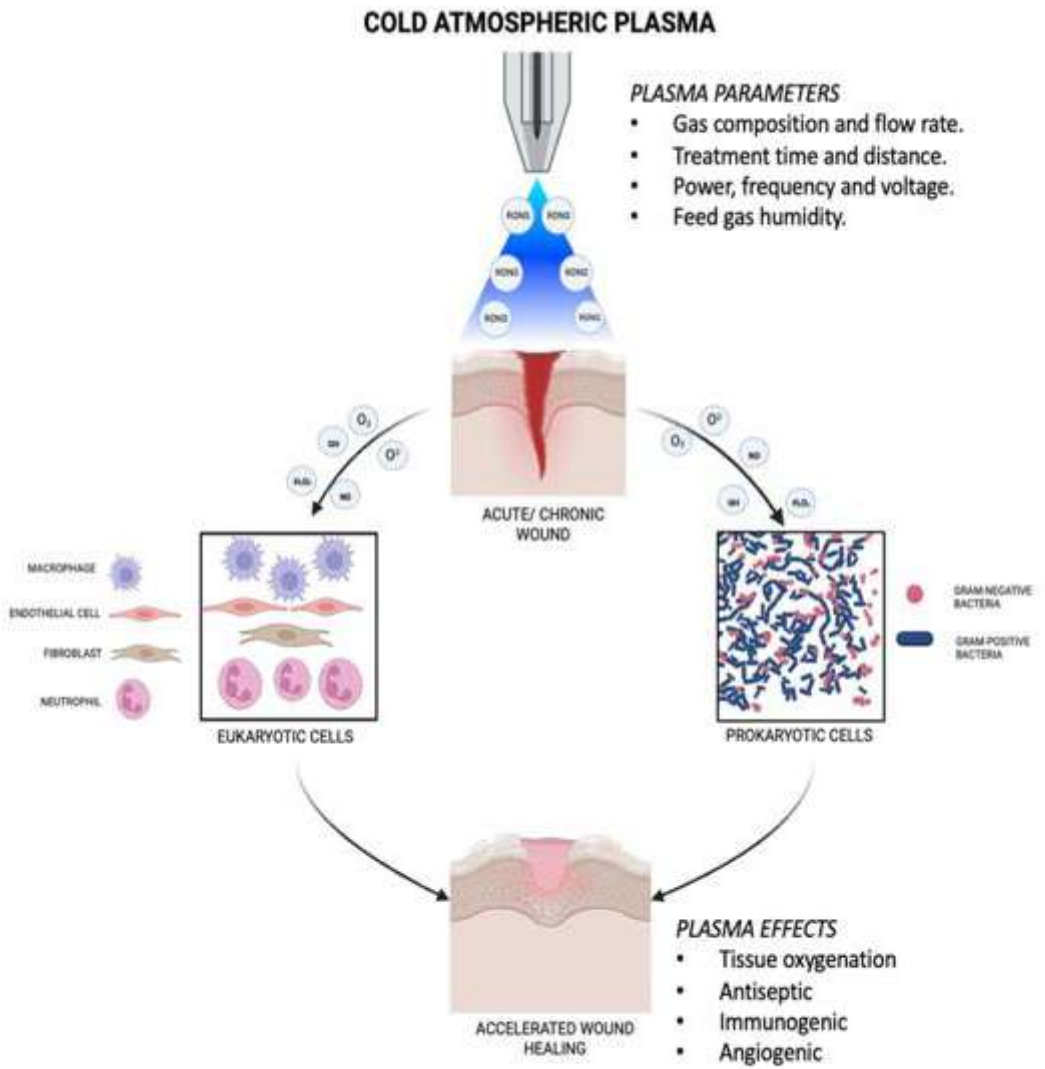
Oda havası sadece oksijenden daha fazlasıdır. Havada çeşitli moleküller vardır, örneğin Oksijen, Azot, Karbondioksit ve Su.



Plasmacure
wound healing

Method of action





Roopak Murali [Cold Atmospheric Plasma (CAP) in Wound Healing: Harnessing A Dual Edged Sword](), Redox Exp. Med, 2023

Dokuda ROS ve RNS etkisi?

Gaz içeriği ve akım hızı

- Helyum, argon ve heliox (helyum+oksijen), azot
- 2.2 lt/dk argon, 2 lt/dk helyum yara iyileşmesi

Temas süresi ve mesafe

- 2-5 dk argon daha iyi yara iyileşmesi
- Mesafe <15 mm daha iyi yara iyileşmesi

Voltaj ve frekans

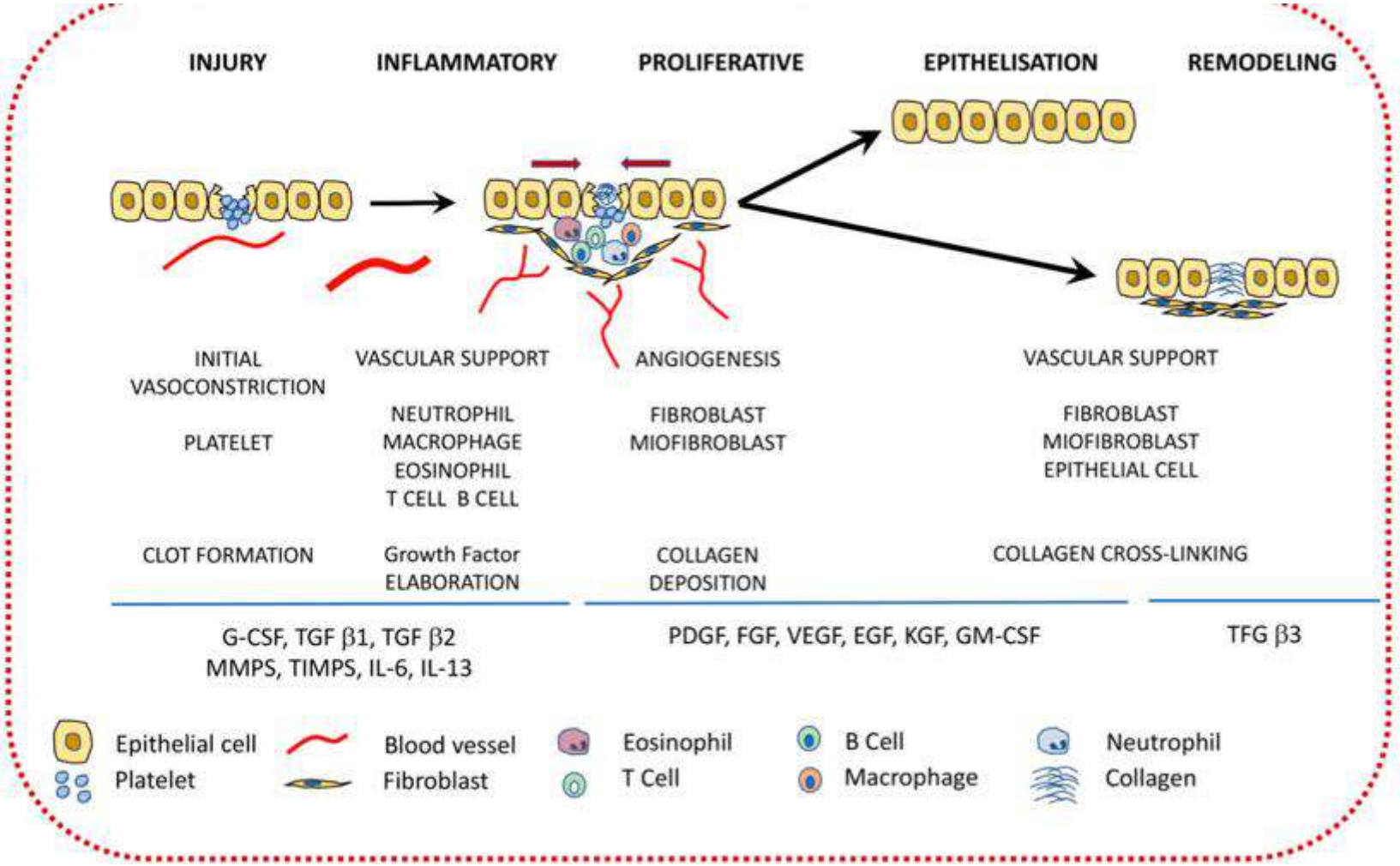
- Voltaj <5 kV, frekans <25 kHz (helyum için) daha iyi granülasyon
- Nemlendirme

Antimikrobiyal etkinlik (standart)

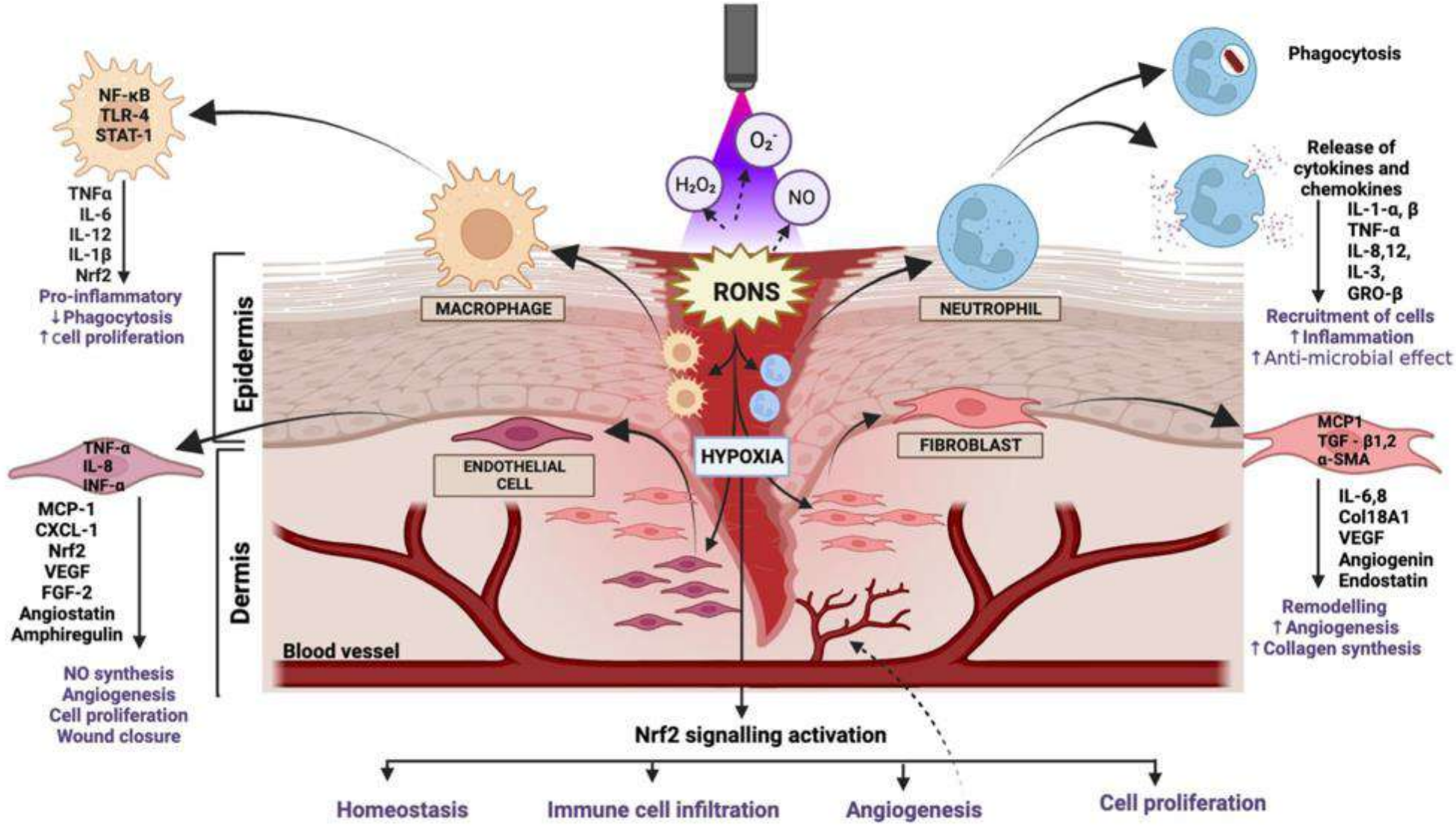
- Lipid peroksidasyonu
- Protein modülasyonu
- DNA hasarı (bakteride-hidrojen peroksit)
- Anti-biyofilm etkinlik

Hangi aşamalarda kullanılabilir?

- Enfekte yarada
- Biyofilm olan yarada
- Granülasyonu başlamış
- Epitelizasyonu kısmi olmuş, durmuş yarada



CAP, yara iyileşmesine etkisi hangi aşamalarda?



Roopak Murali Cold Atmospheric Plasma (CAP) in Wound Healing: Harnessing A Dual Edged Sword, Redox Exp. Med, 2023

Study type	Wound type	CAP device	CAP parameters					Treatment time	Outcome	References
			Frequency	Voltage	Power	FR, slm	Distance[d]			
CT	Chronic ulcers	MicroPlaSter alpha and beta (Argon)	2.6 GHz	50–100 V	86 W	2.2		2-min exposure/day.	Reduced microbial load and increased healing rate of chronic ulcer.	Isbary *et al.* (2012), (2010)
CT	Venous ulcers	PlasmaDerm® VU-2010	50 Hz	230 VAC	8 VA			Average time of 11 min (45 s/cm^2 wound area) per exposure. 3 times a week and for 8 weeks.	Reduced microbial activity and accelerated healing of venous ulcers.	Brehmer *et al.* (2015)
Pilot Study	Atopic dermatitis	MediPL Derm	2.45 GHz ±50 MHz		1.5 W	0.6	5 mm	Plasma exposed for 3 times/day and treated at 0, 1, 2 weeks.	Improved mild and moderate atopic dermatitis and reduced proportion of *Staphylococcus aureus.*	Kim *et al.* (2021)
RCT	Pressure ulcers	Argon Plasma Jet	50 Hz		5[a]; 0.682[b] W/cm^2		5 mm	Plasma exposed at 1 min/cm^2 and once a week for 8 weeks.	Improved PUSH score and reduced bacterial load regardless of the bacterial species.	Chuangsuwanich *et al.* (2016)
RCT	Chronic wounds	SteriPlas® (Argon)	2.6 GHz	50–100 V	86 W	2.2		2-min exposure on the wound site once a week or 3 times a week.	Improved wound healing in patients with therapy-refractory chronic wounds.	Moelleken *et al.* (2020)
CCS	Superficial skin wounds	Plasma Jet		10 kV	50 mW; 5 mA[c]		10 mm	The wound was exposed to CAP for 5 min a day and the procedure was done every 2 days.	Complete healing of the superficial skin wounds irrespective of the type of lesions.	Gao *et al.* (2019)
CCS	Chronic wounds	CPTpatch	NA					2-min plasma exposure 3 times a week, for first 4 weeks and in the next 4 weeks, the plasma was exposed twice a week.	Significant improvement in rate of wound healing as well as reduction in the *Staphylococcus aureus* colony.	Landscheidt *et al.* (2022)
CCS	Psoriasis	PCC	5 kHz	7 kV			1 cm	The psoriasis plaques were exposed to plasma for 30 s for 14 days.	Gradual reduction of psoriasis plaque and complete disappearance on 14th day.	Gareri *et al.* (2020)
RCT	Wounds at donor skin graft sites	Argon Plasma Jet	2.45 GHz		86 W	2.2		The wounds were exposed to plasma for 2 min/day for 7 days.	Rapid healing rate of wounds at skin graft sites.	Heinlin *et al.* (2013)

Study type	Wound type	CAP device	CAP parameters					Treatment time	Outcome	References
			Frequency	Voltage	Power	FR, slm	Distance[d]			
CCS	Ablative CO_2 laser lesions	kINPen®MED plasma jet (Argon)	1 MHz	2–3 kV		4–6		CAP was applied 30 s intervals for 3 days.	Improved rate of wound healing and scar recovery.	Metelmann *et al.* (2013)
RCT	CO_2 laser skin wounds	kINPen®MED plasma jet (Argon)	1 MHz	2–3 kV		4–6		The wounds were exposed for a duration of 60 s to the plasma.	Improved wound healing rate with reduction in redness and roughness of the skin.	Nishijima *et al.* (2019)
CCS	2nd-degree burns	Helium Plasma Jet	13.56 MHz		10 W		5 mm	The site of the burn injury was treated using plasma for 180 s. Two treatments were performed in a single day.	Increased rate of reepithelialization with decontamination of bacteria on the wound sites without any inflammatory effects.	Betancourt-Angeles *et al.* (2017)

[a]Power intensity level; [b]Output power measurement; [c]Discharge current; [d]Distance between lesion and device.
CCS, clinical case study; CT, clinical trial; FR, flow rate; NA, not available; PCC, plasma coagulation controller; RCt, randomized controlled trial; slm, standard liter per minute.

- Kronik yarada farklı yara tiplerinde de başarılı
- Çoğunda yaraya 5mm yakınlıkta
- Çoğunda haftada 3 defa
- Her defasında 2 dk

CAP-sınırlılıkları

- Uzun dönem etkisi tam bilinmiyor?,
- Uygulama etkinliği değişken, hasta seçiminde objektiviteyi bozuyor,
- Hücresel ve doku etkinlikleri gösterilmiş ama vaka çeşitliliği gerekli,
- Argon ve helyum gibi gazların kullanımı bazı ?
- Yanıkta, amputasyon güdüğünde karsinogenezi tetikleyebilir mi?
- Ama …Melanom vb kanser tedavisinde etkin kullanılmaya başlandı?

COLD PLASMA

AN EMERGING TECHNOLOGY FOR CLINICAL USE IN WOUND HEALING

Published by the European Wound Management Association, Nordre Fasanvej 113, 2, 2000 Frederiksberg, Denmark
Web: www.ewma.org. Email: ewma@ewma.org

Journal of Wound Management
EWMA Document 2024

Son nokta …

Hiçbir formu genotoksik değil …

Table 11: Overview of OECD 476 and 487 assays performed with CAP devices.

CAP source type	OECD genotoxicity assay employed	Finding	Reference
DBD operated with Ar	HPRT test	No genotoxicity	377
DBD operated in air	HPRT test	No genotoxicity	361
DBD operated in air	HPRT test	No genotoxicity	212
Atmospheric pressure Ar and neon PJ	MN test	No genotoxicity	378
Atmospheric pressure Ar PJ	MN test	No genotoxicity	379
Atmospheric pressure Ar PJ	HPRT test, MN test	No genotoxicity	380
Atmospheric pressure Ar PJ	MN test	No genotoxicity	381

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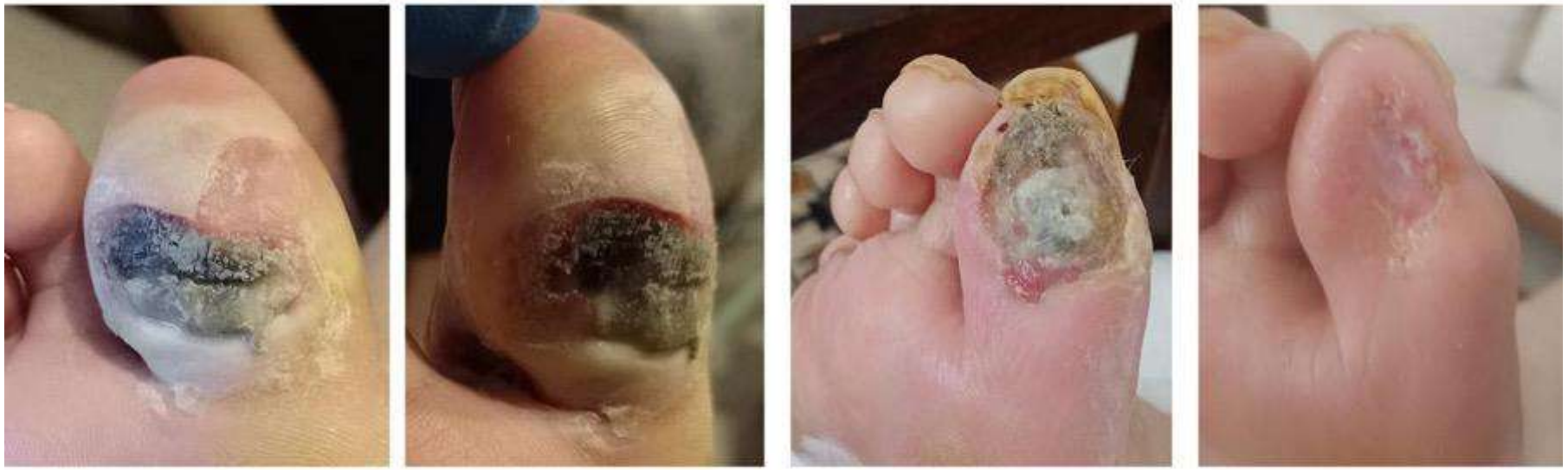
MACRO GENTECH Wound Care

ÖNCESİ/SONRASI

Bifore/After

CASE 8



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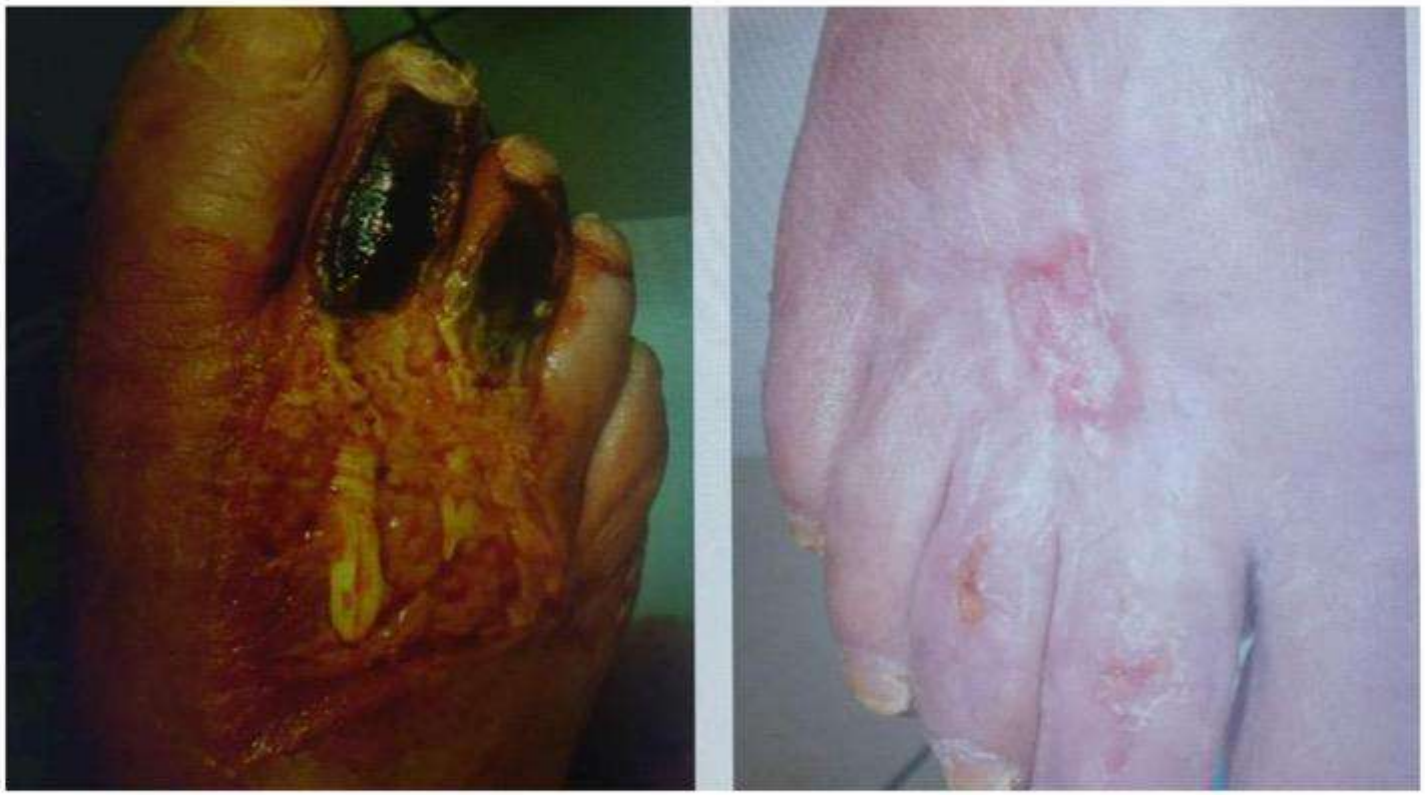
MACRO GENTECH Wound Care

ÖNCESİ/SONRASI

Bifore/After

CASE 17



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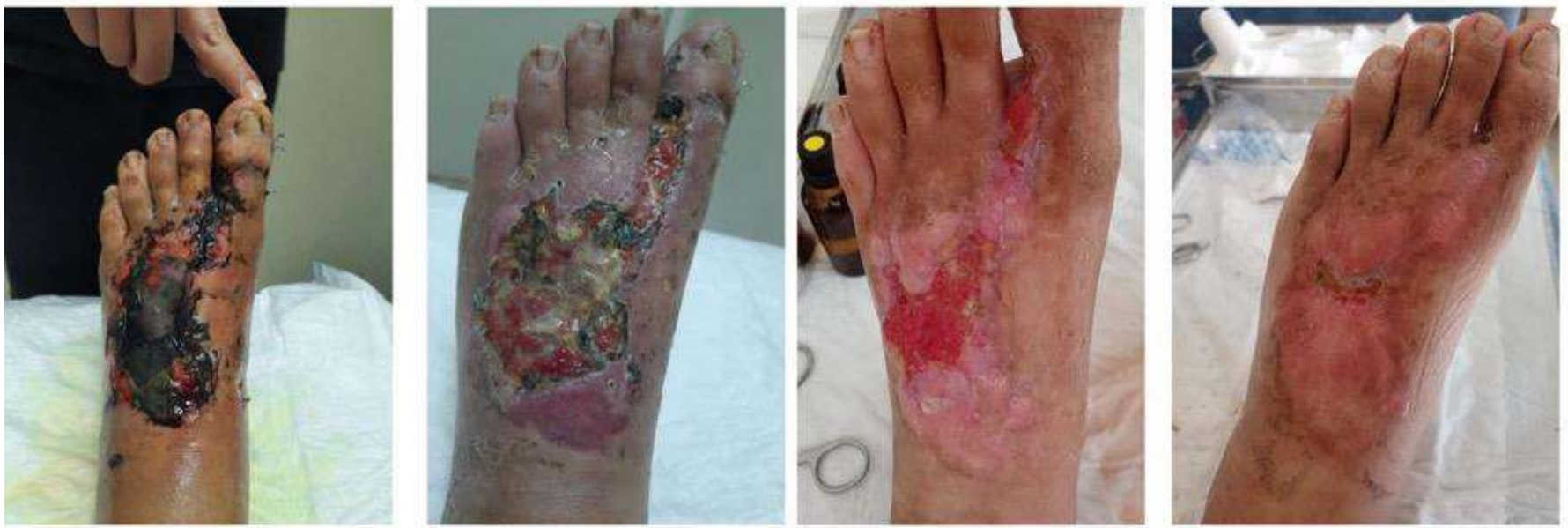
MACRO GENTECH Wound Care

ÖNCESİ/SONRASI

Bifore/After

CASE 7



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